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STUDIES ON THE CEREBRO-SPINAL FLUID AND ITS PATHWAY, NO. IX.*

CALCAREOUS AND OSSEOUS DEPOSITS IN THE ARACHNOIDEA.

By Harvey Cushing and Lewis H. Weed.

(From the Laboratory of Surgical Research, Harvard Medical School.)

Introductory.—In the course of certain investigations undertaken in the laboratory dealing with the cerebro-spinal fluid, special attention has been paid to the determination of the pathway by which the fluid escapes from the subarachnoid spaces into the dural sinuses. It was histologically demonstrated by one of us (Weed, in No. III of the Series,) using a method of injection with subsequent precipitation of granules, that the arachnoid villi or tufts, which though widely distributed project into the dura in greatest number along the course of the larger venous sinuses, represent the chief points of exit for the fluid.

The animals employed for the experiments were chiefly cats, dogs and monkeys, and though macroscopically the meninges appeared normal in every respect, in a small percentage of the specimens the arachnoid showed microscopical evidence of a pathological change, in the shape of small bodies found embedded in the membrane which gave the characteristic tinctorial reactions for calcium. Interest in these bodies was further accentuated by the finding of wholly similar structures in the human leptomeninx where it was possible to trace, often in a single individual, the various stages of their development. We wish to redirect the attention of pathologists to the occurrence of these calcareous depositions and to emphasize their relation to the mesothelial clusters of arachnoid cells incorporated in the dura.

Historical.—Degenerative processes have occupied the attention of pathologists since the establishment of the cellular doctrine and there is an extensive literature on the subject of calcareous degenerations in particular, though the hypotheses regarding this particular form have become modified since the introduction of new viewpoints, particularly of a physical-chemical nature, into cell-chemistry. From Virchow's [22] original dictum that calcification follows upon a local or general disturbance of the nutritive processes of the tissue, some have come to view such a deposition as an evidence of a change in the colloidal reaction of the cell-structures (Lichtwitz [14]). In the interval which elapsed between two conceptions, many observers (Grohe,[10] Hirschberg,[11] Czeck [6] and others) were concerned with the problems of the so-called "Kalkmetastasen" in the sense of Virchow. Still others (notably Gierke,[9] Schmorl,[21] and Hueck,[13]) became interested in the possible

* The previous articles in this series have been published as follows: Numbers I to VII inclusive, Journal of Medical Research, 1914, XXXI, pp. 1-176; Number VIII, American Journal of Physiology, 1915, XXXVI, pp. 77-103.

presence of iron salts in the various calcium depositions in the pathological tissues of the body. And yet another group has attacked the problems of calcification and ossification from the chemical or experimental side (Wells,[24] Moore, Joseph and Williams [17]).

Particular attention has been paid to the occurrence of deposits of lime salts within the cerebro-spinal axis since Virchow called attention to the presence of small calcified bodies in that type of cerebral neoplasm which he designated "Psammome." Not only have these peculiar structures (the so-called psammoma bodies, brain sand, corpora amylacea) been found in the one type of tumor described by Virchow, but they have also been described in practically all classes of slowly developing cerebral neoplasms. In a study of a series of brain tumors, made in Mott's laboratory, depositions of calcium salts were found by one of us [23] in 40% of all cases.

But apart from the occurrence of such degenerative processes in the cerebral new growths, the deposition of calcium salts appears to be a normal physiological phenomenon in two adult human structures within the central nervous system, the corpus pineale and the plexus choroideus. Meyer [16] has differentiated morphologically the calcified bodies in these two situations and has shown that the neoplasms arising from them contain the typical form of calcareous bodies found in the gland of origin. In a discussion of calcification and its occurrence in various tissues other than in the pineal gland and choroid plexus, von Recklinghausen [20] called attention to the localized calcareous granules in the meninges, but gave no detailed account of the process. True bony growths in the shape of osteophytes arising from the meninges are of frequent occurrence and osseous deposits in the arachnoid in the form of plaques have been repeatedly recorded, for the most part, as unimportant descriptions of individual cases (Brinton,[3] Burton,[4] Evans,[7] Potts,[19] Fletcher [8]). But if one agree with Paulicki,[18] who long ago differentiated calcification from ossification on the basis that the former represents a degenerative process, while the latter is solely hyperplastic as evidenced by the vascularization and proliferation of osteoblasts, the reports in the literature concerned with meningeal calcification as a separate process have been few.

Probably the two most important communications dealing with calcification in the arachnoid are those of Zanda [25] and of Levi.[13] The former made studies of the osteomata arising from the spinal arachnoid with especial reference to their stages in development and to the subsequent vascularization. On the inner surface of this leptomeninx near the site of the outspoken osseous tumor, he observed distinct nodules which varied in size from those barely visible to the unaided eye to masses several millimeters in diameter. Microscopically, they were composed of concentric layers of cells in the midst of similar circular strands of connective tissue, while in the center of each mass was found a calcified body, usually exhibiting characteristic concentric rings. From this elementary stage, Zanda traced the subsequent osteoma through a formation of sclerotic rings of connective tissue about the primary calcareous body to a final vascular invasion of the increasing calcified area by vessels coming from the dura. Of interest in our problem is Zanda's division of the primary calcified bodies into those which arise from the connective-tissue fibers and those which apparently come from cells.

Levi,[13] in an excellent inaugural dissertation, dealt with the occurrence and the significance of calcified concretions in psammoma tumors as well as in the plaques which occur in the spinal arachnoid. In the cerebral neoplasms, he observed a cellular reaction or hyperplasia about the calcified body, and suggested that the calcium salts were for the most part laid down in degenerated cells. In the plaques found in the spinal arachnoid, the cases apparently fell into the two classes proposed by Zanda; in one, the calcium deposition occurred in the midst of an endothelial cell hyperplasia, while in the other the lime salts were found in the connective-tissue strands composing the trabeculæ of the arachnoidea.

Personal Observations on Calcified Bodies in the Arachnoid.—Our attention was first directed, in 1912, to microscopic abnormalities in the arachnoid membrane in healthy animals by the observation of a peculiar proliferation of the arachnoid mesothelium in the meninges of a cat. The animal was a young adult, whose brain and cerebral meninges had been sectioned for study of the meningeal relations in the region of the superior longitudinal sinus. Similar hyperplasias of the arachnoidal mesothelium were occasionally encountered in the course of our studies of the next two years, during which period many specimens of the arachnoid, both of man and also of the lower animals, were serially sectioned. Though our chief concern lay with the structure and function of the normal arachnoidal villi which penetrate the dura, our interest was naturally extended to this proliferative process occurring in the cells composing these structures. Though the proportion of laboratory specimens in which we observed examples of cellular hyperplasia was small, the process was almost invariably associated with the deposition of lime salts in the membrane, and many of the stages in the formation of the calcareous masses have been observed.

The general process of calcification in the arachnoid must necessarily differ somewhat from that in other portions of the organism, for in this structure we are dealing with a membrane, whose nutritive exchanges are derived from the circumambient cerebro-spinal fluid rather than from the circulating blood. Again the process is modified somewhat by the fact that the connective-tissue elements of the arachnoid are slight in amount and quite insignificant as compared to the mesothelial cell clusters which surmount the arachnoid villi.

The initial step in the formation of calcium depositions in the arachnoid appears to be a proliferation of the mesothelial cells of the membrane. Such a hyperplasia is usually best seen in the neighborhood of the arachnoidal tufts or villi which, as is known, project into the dura, particularly in the region of the great sinuses.

Stages of the degenerative process commonly observed in these cell clusters are illustrated in the first six figures. In Fig. 1 is shown a clumping of the nuclei in a small cell cluster on the outer surface of the arachnoid membrane of a cat. In

this clump of nuclei, the typical chromatin masses and strands which characterize a normal nucleus, have been lost and, although the external nuclear form is retained, a homogeneous mass appears. The process is associated with an infiltration of calcium salts, definitely limited to the small clump of arachnoid cells, the test of calcification in this as in all cases being the characteristic staining reaction with hematoxylin confirmed by silver nitrate reductions. The nuclear forms stand out distinctly from the remainder of the infiltrated area, suggesting that there is either a primary deposition of calcium in the nuclei or that they possess a greater affinity for the circulating calcium in solution. The arachnoid cells and stroma of the surrounding membrane appear normal in every respect.

An intradural invagination of hyperplastic arachnoidal mesothelium of larger size, which has undergone much the same degenerative change, is shown in Fig. 2 taken from the meninges of a dog, the nuclei of the cells having lost their intranuclear structure with subsequent deposition of calcium elements. The sparse internuclear substance has also been infiltrated, though to a lesser degree, with similar salts, the nuclear outlines being still apparent even though both nuclei and scanty cytoplasm have become calcified. No calcium deposits can be made out in the true dural tissues except in relation to the arachnoid cell-column. Along the periphery of the degenerated cells may be seen other nuclei of leptomeningeal origin which appear to be normal in character.

In Fig. 3 there is shown a small area of arachnoid tissue within the dura, which contains, arranged in the form of a circlet, a small number of calcified bodies, resembling in their external form and size typical arachnoid nuclei, but showing no intranuclear morphology. The degenerative process seems to be limited, as far as the infiltration with lime salts is concerned, solely to these minute nuclear-like masses. The intercellular substance and the cytoplasm are wholly unaffected by the calcium depositions. The rosette of calcareous bodies surrounds a small area which has apparently undergone slight homogeneous degeneration but without any invasion by lime salts. About this peculiar degenerated area are normal strands of dural fibers.

An interesting finding in the canine meninges, shown in Fig. 4, suggests a primary deposition of lime salts in other elements than the nuclei, which therefore need not be the sole factors in this process. In the midst of the arachnoid membrane occurs a small collection of normal arachnoid nuclei surrounding an area in which calcium salts have been deposited in tiny round and oval forms. These bodies are much smaller than the nuclei and between them there is a suggestion of a diffuse calcium infiltration.

Thus far we have been concerned solely with minute depositions of calcium salts and not with outspoken psammoma bodies or large plaques. In the series of the leptomeninges of man and of the lower animals, much larger calcareous areas have been found. Thus in Fig. 5 (from a cat) and Fig. 6 (from a monkey) there appear circumscribed calcified formations, which are limited to the arachnoid areas whether merely in apposition with the dura or incorporated within it. In some of the bodies the tinctorial reactions for calcium are not marked; in others the infiltration is dense and sharply delimited. The number of the cells enveloping these calcareous centers varies greatly in the specimens as also does the more or less marked tendency to whorl formation on the part of the cells; but in all cases the association of the calcified deposits with arachnoid mesothelium is unmistakable.

This may be more clearly brought out by the section in Fig. 7, taken from the meninges of a man. Here is shown an arachnoid villus which projects through the dura into the sagittal sinus. The brain from which the specimen was taken had been under a long-standing pressure and consequently the villus appears distended and the outer layer of the arachnoid considerably thickened. Stages of the process to which we would call attention appear in the higher magnification of the blocked areas at A, B, C, and D. In Fig. 7A is a cluster of arachnoid cells which have undergone hyperplasia and which show the characteristic whorl formation commonly seen in the so-called dural endotheliomas. There is no tinctorial evidence of calcium deposition. Such a deposition does appear, however, in Fig. 7B, where in addition to whorl formation there is a sharply cut sand body. In Fig. 7C is another cluster of hyperplastic mesothelial cells lying at the neck of the arachnoid villus where it penetrates the dura, its appearance resembling closely the group of cells in Fig. 2, although no calcium deposition has occurred. Another sand body in process of formation with ghosts of nuclei still discernible appears in Fig. 7D, where it lies in a cluster of cells on the margin of the free arachnoid lining the subdural space.

The internal structure of the calcium body is always of interest, for in the more minute forms no obvious key to the method of deposition can be made out, whereas, in the larger depositions, each successive calcareous increment seems to have been recorded. The bodies thus formed may be lamellated and exhibit concentric rings resembling starch granules; or when the deposition is more irregular, amorphorous concretions arise. The terms *corpora amylacea* (starch bodies) and *corpora arenacea* (sand bodies) are still often used interchangeably and were originally regarded even by Virchow as similar structures, until he demonstrated that they were distinguishable by the iodine reaction.

One of the most perplexing of the questions related to these depositions of calcium concerns the cellular increase which may be observed in practically all cases. Levi [13] and Zanda [25] have both described this phenomenon, but have not discussed its significance. Is this cell-proliferation the essential basis for the calcification or is it merely a reactive phenomenon as that against some foreign substance? Certainly in the fully developed cases of calcareous deposition, the cell reaction might appear to be wholly secondary to an original degenerative change. But this explanation for the cell-proliferation will not hold, as a general rule, when one examines the stages in the formation of such calcified bodies. The proliferation of arachnoidal mesothelium with a tendency to form whorls is not uncommon, and areas of the hyperplastic cells, associated in no way with degenerative changes, are often found in the dura.

Thus, in Fig. 7-A, can be seen an arachnoid cell-mass with the nuclei and internuclear material concentrically arranged, analogous in every respect to the cellular proliferation seen in Fig. 6, which surrounds a calcified body.

If one were to assume the cellular proliferation to be a reaction secondary to the calcium deposition, it should occur with some regularity, but in many of the specimens, there is but little tendency for a cellular hyperplasia to occur about the area of calcification. On the whole the evidence indicates that the cellular proliferation is not a phenomenon expressing reaction to the foreign body.

What, then, are the basic elements in which such calcareous depositions occur in the tissues within the dura? Many points of origin for psammoma bodies and for brain sand have been suggested in the past. Von Recklinghausen [20] believed that these minute calcareous bodies arose from sclerotic connective tissue in the various tumor forms within the nervous system. He premised that an increase in the cells on the periphery followed the deposition of lime salts in the center. Bizzozero [2] described hyaline bodies, possibly of nuclear origin, which may be the substance in which the lime salts are deposited. Quite in accord with these observations are the two divisions of the bodies made by Zanda [25] and corroborated by Levi. [13] The calcareous masses in the arachnoid may, according to these observers, arise either from arachnoid cells which have degenerated, or from the sclerotic connective tissue comprising the arachnoidal trabeculæ.

Quite opposed to these views of the cellular origin of the smaller calcareous concretions are the observations of Arnold,[1] of Cornil and Ranvier,[5] of Mallory [15] and others. These observers have reported findings arguing for a vascular origin of the sand-like bodies. Arnold first noted a petrifying hyaline degeneration in the lumina of the smallest vessels in a psammoma. Somewhat similarly, Cornil and Ranvier observed phleboliths in the vessels of the choroid plexuses, identical in morphology and appearance with the granules known as brain sand. Mallory's description of calcification of the cerebral capillaries in the basilar nuclei also favors this idea of a vascular origin. One often sees, particularly along the course of the vessels in the granular layer of the cerebellum, small masses of hyaline which may lead to the occlusion of the vessels and often become calcareous. These formations, however, rarely are concentric, and there seems to be no relation between this process and the spherical and concentrically disposed psammoma bodies; and the same may be said of the irregular calcification of hyaline in gliomas. Mallory's conclusions that a vascular basis underlies the formation of these bodies surely cannot account for the depositions in non-vascular areas with which we are chiefly concerned. In short the stages in the formation of the calcareous deposits in the arachnoid indicated a cellular rather than a vascular origin for the primary infiltration. The vascular conception finds but little support except in the general appearances of the cellular whorls, for the membrane, though it carries vessels, is without capillaries and derives its nutrition from the circumambient cerebro-spinal fluid. In the earliest stages the nuclei, almost to the exclusion of the cytoplasm, seem to be affected by the calcareous change. Whether this is due to the initial degeneration of the nuclear material or to a greater affinity of the lime salts for the degenerated nucleus, cannot be told.

Observations on Osseous Deposits in the Arachnoid.—The close association of the small calcareous depositions with the cells of the arachnoid membrane holds true also for the analogous areas of ossification in this membrane. Chemically, there seem to be "no essential differences between the processes involved in normal ossification and in most instances of pathological calcification" (Wells [24]), but biologically the latter appears to be degenerative and the former proliferative (Paulicki [18]).

The majority of the reports which deal with bone formation in the arachnoid describe the plaques in the spinal meninges, though there occur a few descriptions of growth of bone in the cerebral arachnoid (Fletcher,[6] Evans,[7] and others). As Virchow long ago pointed out in his justly celebrated lectures on tumors, these plaques were long erroneously regarded as the cause of epilepsy, chorea, tetanus, and other convulsive disorders.

It would seem that the process is more common in the membranes of the cord: at all events one encounters at operation small ossified bodies adherent to the spinal arachnoid more often than in the corresponding covering of the brain. One notable example, however, of ossification of the cerebral arachnoid has recently come under observation in a boy suffering with epilepsy. He had been the victim in early life of a severe infection, presumably a meningo-encephalitis, and at the operation, after an apparently normal dura had been reflected, the thickened arachnoid was found covered with large plaques of thin bone, some of which (shown in Fig. 8) were capable of being stripped away without causing bleeding. The minute spinal plaques which we have seen have likewise been deposited in membranes which had formerly been the seat of an inflammatory process.

In Fig. 9 is shown another example of bone deposition. This occurred as an osseous nodule in the falx of a patient who had a coincident pituitary tumor. More or less isolated nodules of this sort—really osteophytes—are not at all infrequent postmortem findings and curiously enough, as has been long recognized, they are practically confined to the falx.

Still another example of true bone formation in the meshes of the human arachnoid is shown in Fig. 10. The coronal section includes the sagittal sinus at about the vertex and the wide-spread distribution of the deposits are apparent in the low-power drawing. They are of variable size; the largest is about 6 mm. in its long diameter and, as can be seen, it has served to displace the cortical tissue. The deposits are composed of true bone, as is evidenced by the occurrence in them of the typical lacunar systems, Haversian canals, and the characteristic osteoblasts and osteoclasts. Necessarily, they are vascularized, thus affording a marked distinction from the calcareous concretions which have already been discussed.

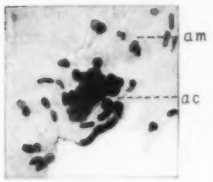


FIG. 1.

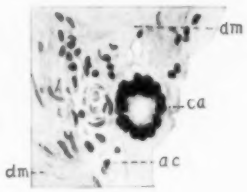
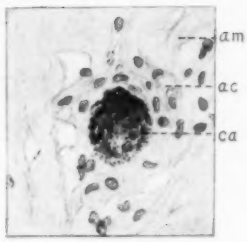


FIG. 3.



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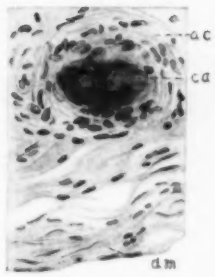


FIG. 5.

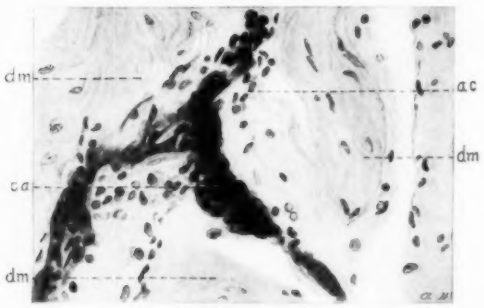
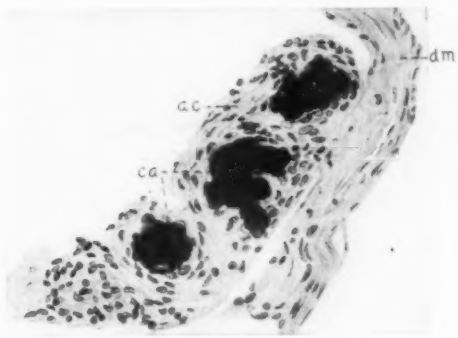


FIG. 2.



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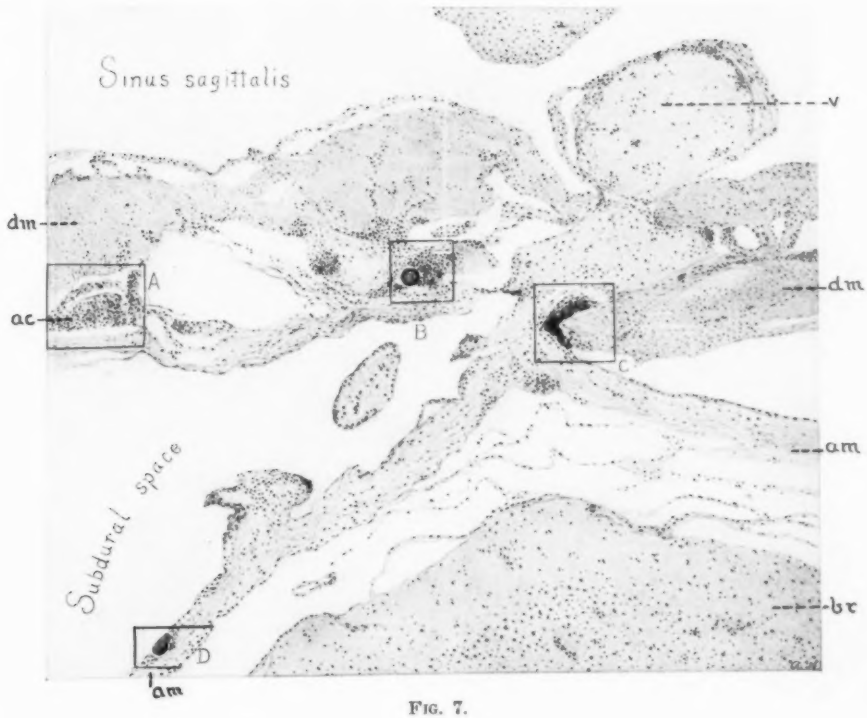

FIG. 7.

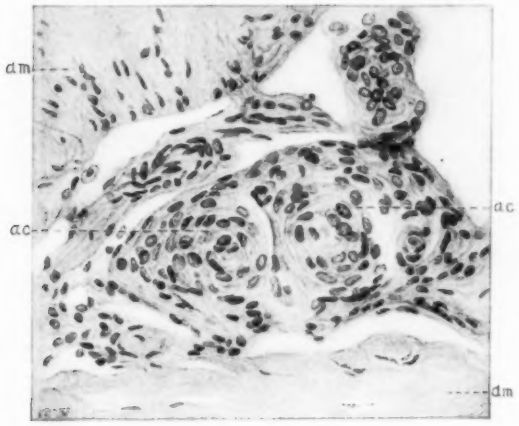

FIG. 7A.

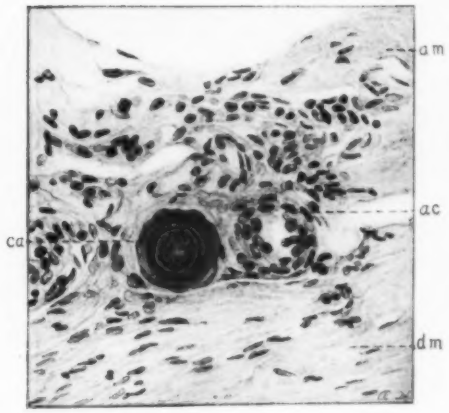

FIG. 7B.

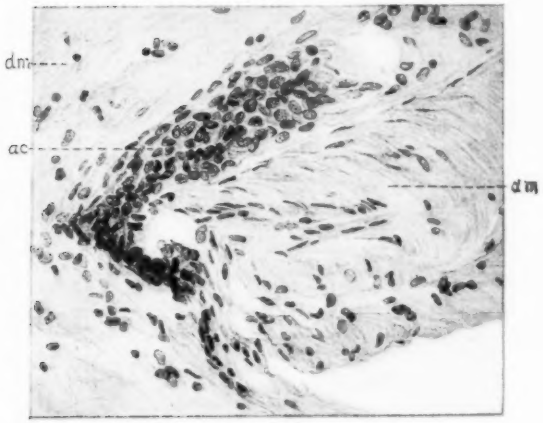

FIG. 7C.

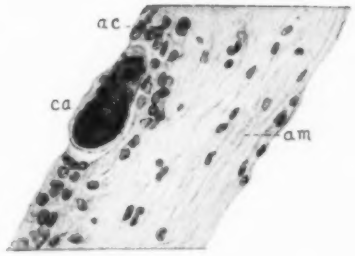

FIG. 7D.

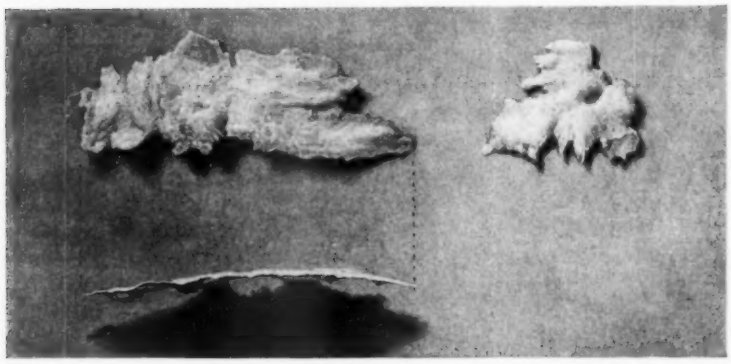

FIG. 8.

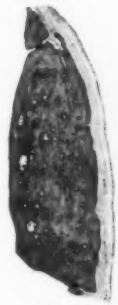

FIG. 9.

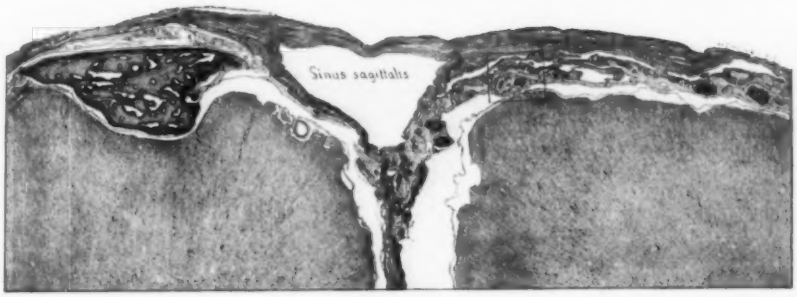

FIG. 10.

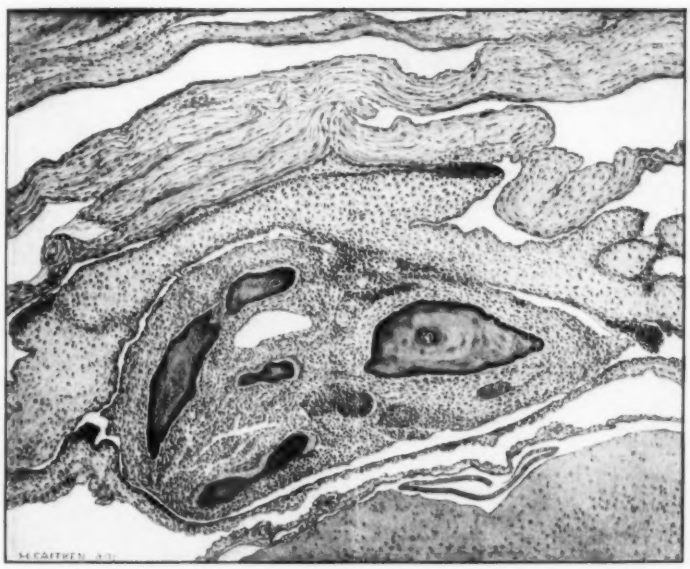

FIG. 11.

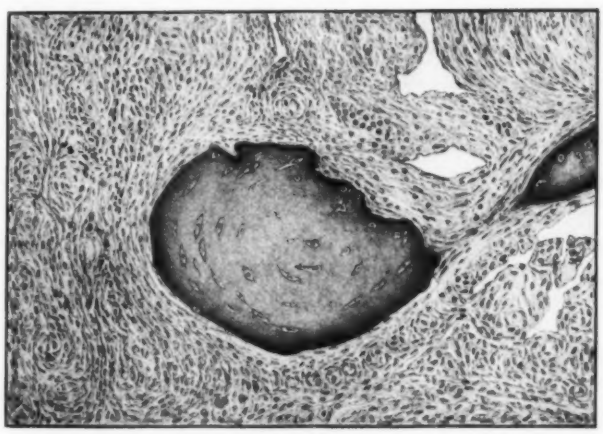

FIG. 12.

One important feature of the osseous nodules lies in their relation to the surrounding tissue. In the low-power drawing (Fig. 10) the deposits appear to lie just beneath or within the dura, but under higher magnification (Fig. 11) the areas of bone are seen to lie in the midst of a very cellular mass. The general appearance of these cells, their situation and their relation to the surrounding dense strands of dural tissue mark them as undoubtedly arachnoidal in character. The hyperplastic appearance of these arachnoid cells, moreover, suggests in every way the cell clusters which were shown to be often associated with the calcareous bodies. It would, therefore, appear that, as the result of similar influences, the arachnoid may become involved in the two processes. Levi and Zanda have both described the cellular proliferation about the bony and calcified deposits in the spinal arachnoid, and it would seem that this is also to be found in the brain.

Whether this cellular hyperplasia of the arachnoid mesothelium is a precursor of the bone formation, or merely a secondary reactive phenomenon, is as difficult to decide as in the case of the calcareous deposits. Whether or not one is to be looked upon as a degenerative and the other as a proliferative process, the evidence on the whole suggests that the calcification and ossification depend on some underlying cause, which primarily or secondarily is accompanied by a proliferation of mesothelial cells.

These arachnoidal structures have the same histological ground-work which appears in the meningeal fibro-endotheliomas, and it is our impression that these tumors arise from the mesothelium of the arachnoid and not from the dura, as is commonly believed. The sections (Figs. 7 and 10) from the human brain were taken from cases in which there were a coincident fibro-endothelioma, and it is to be noted that in these mesothelial tumors, cellular whorls, psammoma bodies and true bone depositions, as shown in Fig. 11, frequently occur. This will be dwelt upon in further detail in a future communication.

SUMMARY.

Calcareous depositions in the form of psammoma bodies, or *corpora amylacea* of varying stages of development and of varying size, are of common occurrence in the arachnoidea of man and of the lower animals. Associated with this process of calcification there is apt to occur a hyperplasia of the arachnoidal mesothelium. The deposits of lime salts are apparently laid down in cell-bodies and in this membrane can bear no relation to the blood vessels.

The occurrence of true bone formation in the arachnoid of man should be regarded as a similar phenomenon, except that one may consider the process of ossification to be proliferative rather than degenerative.

The so-called dural endotheliomas show histologically the same cellular arrangements with calcareous and osseous depositions that are commonly found in the arachnoid and therefore take their origin in all probability from the mesothelium of this membrane.

KEY TO FIGURE LEGENDS.

ac=arachnoidal mesothelial cells
am=arachnoid membrane
br=brain
ca=calcareous deposition
dm=dura mater cerebri
v=villus

DESCRIPTION OF PLATES.

FIG. 1.—Drawing of coronal section of the arachnoid membrane (am). In one area a clumping of nuclei is made out; many of these have undergone a degenerative change with infiltration of lime salts. In others, some of the intranuclear morphology is still retained. From a cat. (× 315 diam.)

FIG. 2.—Coronal section showing an arachnoid invagination (ca) within the dura (dm). The column of nuclei has undergone partial calcification. There is some deposition of lime salts in the inter-nuclear substance. On the periphery of this degeneration column, normal arachnoid nuclei (ac) are made out. From a dog. (× 315 diam.)

FIG. 3.—From a coronal section of a lateral wall of the superior longitudinal sinus of a cat. A portion of an arachnoidal cell-column or villus is shown surrounded by dural tissue (dm). A chain of oval arachnoidal nuclei appear, grouped around a small blood vessel. The arachnoid nuclei, arranged in one area in a circlet, have become infiltrated with calcium salts (ca) and no longer show any intra-nuclear morphology. (× 315 diam.)

FIG. 4.—From a coronal section of a canine arachnoid membrane near the superior longitudinal sinus. In the midst of the delicate reticulum of the membrane (am) is a collection of typical arachnoid cells (ac) which surround a slight calcareous deposition (ca). (× 315 diam.)

FIG. 5.—From a coronal section: monkey. The dura (dm) shows its normal fibrous character. The arachnoid tuft consists of concentric layers of cells (ac), within which the characteristic infiltration with calcium salts is apparent. (× 315 diam.)

FIG. 6.—From a coronal section: dog. A cellular hyperplasia is everywhere in evidence in the arachnoid cells (ac); in some areas these cells surround masses in which calcareous infiltration (ca) has occurred. The dura (dm) is normal. (× 315 diam.)

FIG. 7.—From a coronal section showing the lateral wall of the superior longitudinal sinus with adjacent meninges and cortex cerebri, in the region of the fissure of Rolando. Note the invasion of the dense dural strands elsewhere by arachnoid structures in which calcareous depositions and cellular hyperplasias occur. From a man. (× 60 diam.)

FIG. 7A.—Higher magnification (315 diam.) of area A, in Fig. 7. The proliferation of arachnoidal cells (ac), arranged in concentric whorls, is shown in the midst of dense strands of dural connective tissue (dm).

FIG. 7B.—Higher magnification (315 diam.) of area B, in Fig. 7. In the midst of a collection of arachnoid nuclei is shown a psammoma body (ca), the internal structure of which resembles that of a starch granule. There is no cellular hyperplasia about the body, but in its immediate vicinity there is a typical whorl of arachnoid cells (ac). Surrounding the cellular area, the strands of dural tissue (dm) appear.

FIG. 7C.—Higher magnification (315 diam.) of area C, in Fig. 7. A marked collection of arachnoid cells (ac) is shown in the midst of the connective tissue strands of the dura mater.

FIG. 7D.—Higher magnification (315 diam.) of area D, in Fig. 7. A calcareous concretion (ca) occurs on the outer portion of the arachnoid membrane (am), with but slight proliferation of arachnoid cells (ac) about it.

FIG. 8.—Ossified plaques from the cerebral arachnoid of a man. (Normal size.)

FIG. 9.—Osteophyte from the falx of a man. (× 10 diam.)

FIG. 10.—Coronal section from a man showing multiple foci of bone formation in the arachnoid. From a patient with an endothelioma of the temporal region (cf. Fig. 12.)

FIG. 11.—Higher magnification of squared area in Fig. 10.

FIG. 12.—Meningeal endothelioma containing foci of ossification (cf. ossification of meninges elsewhere in the case Fig. 10). (× 100 diam.)

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THE CALCIUM FACTOR IN HEMOPHILIA.

A CASE WITH CALCIUM DEFICIENCY (CALCIPRIVA).*

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Ever since it has been known that calcium plays a significant part in the normal clotting of the blood, investigations have been carried out to determine whether a lack of this substance could account for the delay in coagulation in hemophilia and in other hemorrhagic diseases. The results of these investigations have led in general to the conclusion that a lack of calcium does not enter into the pathogenesis of hemophilia, and perhaps has little relation to this entire group of diseases.[1,2] The method pursued in such studies has been the simple one of adding a dilute solution of calcium to the blood and noting whether this addition shortened the clotting-time. The addition of calcium has been found not only not to hasten coagulation, but even to delay it. The present paper goes into this question of calcium deficiency somewhat more fully. We are able to report a case of hemophilia, in which the calcium was determined not only functionally by the simple method just mentioned, but also by means of a direct estimation of the calcium of the blood, and a study of the calcium metabolism balance. In connection with this study we were able to pursue a similar investigation in a case of typical hemophilia. As far as we are aware, there have been no previous metabolism studies in this condition.

The child (Alter) is six years old and has been under our observation at the Hebrew Infant Asylum for the past three years. During the past year, and even longer, numerous coagulation tests of his blood have been made, and his general health has been carefully watched. Attention was first directed to him on account of his tendency to bleed from minor cuts, to manifest frequent "black and blue marks," and to have severe hemorrhages from the nose. As far as can be ascertained, he is the sole member of his family who is a bleeder, so that we must consider him as affording an instance of the sporadic type of hemophilia. He is fairly well nourished, weighs about fifty pounds and shows no other abnormality except a moderate degree of ichthyosis of the skin. This abnormality acquires additional interest owing to the fact that, like hemophilia, it is

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a disease which occurs in the male and is transmitted by the female. Color blindness, to which this law of heredity also applies, was not present.

When his blood was first tested in the spring of 1914, the plasma was found to take 58 minutes to clot. The normal clotting-time is from about six to ten minutes. For this test the method of Howell [3] was employed, which consists of adding one to five drops of a 0.5 per cent solution of calcium chloride to oxalated plasma. About one month later the plasma coagulated in 16 minutes. The variations in this regard during the past fifteen months, as may be seen from the accompanying table (Table 1), have been most marked. Recently, this summer, we

TABLE 1.—CLOTTING TIME OF PLASMA AND OF BLOOD. CALCIPRIVA CASE.

Date.	Plasma coag.-time.	Blood coag.-time (10 drops).	Remarks.
4-21-14	58 min.	29 min.	Control plasma clotted in 8 minutes.
5-21-14	16 min.	11.5 min.	Frequent nose-bleed. Hematoma over frontal bone.
5-23-14	30 min.	....	Plasma to which 6 drops of calcium were added clotted first.
5-26-14	28 min.	....	Tubes Nos. 5 and 6 clotted first. Nos. 1 and 2 did not clot.
5-28-14	28 min.	....	
6-15-14	22 min.	....	
6-25-14	18 min.	....	
8-19-14	12 min.	10 min.	Subcutaneous hemorrhages, and oozing from wound of finger.
8-24-14	12 min.	....	Calcium and magnesium have been given for metabolism tests.
8-31-14	12 min.	....	One drop of normal antithrombin permanently prevented blood from clotting, whereas control clotted in 10 minutes.
10- 7-14	....	19 min.	Bleeding from finger.
10-24-14	....	15 min.	
10-27-14	....	15 min.	Nose-bleed 48 hours ago.
11-10-14	32 min.	15 min.	Has received calcium for past 4 days.
11-17-14	34 min.	....	
12- 2-14	12 min.	7 min.	Has received calcium lactate for some weeks. Adding of calcium to blood postponed clotting, as it did also two weeks later.
6-26-15	88 min.	....	General condition not so good.
7- 2-15	60 min.	....	
7- 9-15	....	34 min.	12 drops of blood used. Addition of calcium reduced clotting-time to 13 minutes. Test reproduced in Table 1.
9- 8-15	22 min.		Platelets 516,000.

were surprised to find that the plasma once more clotted slowly, in fact that it had reached its lowest level, taking eighty-eight minutes to form a firm clot. In another column of this table will be seen the clotting-time of the unaltered blood—the period it took for ten drops of whole blood to form a clot in a clean vial having a diameter of 1.5 cm. We are unable to account for the marked variation in the coagulation time of the plasma. The hastening was not due to previous loss of blood, as is so commonly the case in hemophilia, but seemed rather to run parallel to the general physical improvement of the child.

In view of the fact that at times, as may be noted, the plasma of this boy clotted almost within the normal limit, a characteristic of purpura in contradistinction to hemophilia, it may be questioned why we regard this case as an instance of hemophilia. In the first place, the coagulation time has occasionally been so greatly delayed that in this respect the case corresponded with one of hemophilia. Furthermore, a deficiency of blood platelets, the typical characteristic of purpura, was not found at any time; the counts at various intervals being 310,000, 487,000, 463,000. Increased pressure upon the blood vessels did not lead to the appearance of petechial hemorrhages as in purpura. This test which we have described elsewhere [4] as the "capillary resistance test," consists in placing a tourniquet about the upper arm for a definite period, and noting whether this pressure leads to the appearance of petechiae upon the forearm. Again, the hemorrhages in this instance were fairly characteristic of hemophilia—they were large, not pinpoint, and occurred at times into the joints, for example, as hemarthros of the hip and of the ankle-joints. A consideration of these various phenomena would seem to justify our classifying the case as one of hemophilia.

In the course of a series of tests consisting of the addition of small amounts of calcium solution to the blood, we noted that this case reacted differently from those of other hemophiliacs,

TABLE 2.—EFFECT UPON CLOTTING-TIME OF ADDITION OF CALCIUM SOLUTION TO BLOOD.

A. NORMAL CASE.

Clotting-time.	Control.	Drops of Ca solution added.			
		1	2	3	4
4 min.	+	....	+	+	+
5 min.	++	....	++	++	+
6 min.	+++	....	+++	++	++
7 min.	....	....	....	++	++
9 min.	....	....	....	++	++
11 min.	....	....	....	++	++
13 min.	....	....	....	++	++
15 min.	....	....	....	+++	++
17 min.	....	....	....	....	++

B. HEMOPHILIA CALCIPRIVA (ALTER).

5 min.	—	—	—	—	—
9 min.	—	—	—	—	—
11 min.	—	+	++	—	—
13 min.	—	+	+++	+	—
17 min.	—	+++	....	++	+
21 min.	—	....	....	++	++
26 min.	+	....	....	+++	+++
34 min.	+++	....	....	....	....

C. TYPICAL HEMOPHILIA.

4 min.	—	—	—	—	—
8 min.	—	—	—	—	—
10 min.	+	++	+	++	+
14 min.	++	++	++	++	++
18 min.	+++	++	++	++	++
22 min.	....	++	++	++	++
26 min.	....	++	+++	++	++
30 min.	....	....	....	+++	++

+++ denotes complete clotting-time.

in that coagulability was hastened by the calcium. In view of the quantitative determinations of the calcium of the blood, which will be considered below, we decided to make use of a solution of calcium chloride weaker than the 0.5 per cent commonly employed for recalcifying plasma, and accordingly prepared for this purpose a solution containing 0.04 gm. of CaO per 1000 parts of normal salt solution. This strength was selected because one drop corresponded approximately to the deficiency of calcium which had been ascertained to exist in the blood. An illustration of the results of adding this weak calcium solution to the blood may be seen in Table 2. It will be noted that the normal blood, which coagulated in six minutes, was not hastened by the calcium, that a case of typical hereditary hemophilia likewise remained unaffected, but that the blood of this boy (Alter, July 9, 1915) coagulated more than twice as rapidly upon the addition of the calcium. This result was repeatedly obtained, as may be seen in the remarks in Table 1; the only exception to this rule was in December, after he had been fed on calcium lactate for some weeks and his blood probably had absorbed its optimal amount of calcium.

A functional deficiency of calcium having been definitely established in this case, Dr Max Kahn tested the blood for its absolute content of calcium. For this purpose McCrudden's method[5] was employed, which enables one to determine the amount of calcium in even less than 10 cc. of blood. These determinations, which were made with from 6 to 10 cc. of blood aspirated directly from the vein, are reproduced in Table 3.

TABLE 3.—CaO IN BLOOD.

Normal controls.	Hemophilia calcipriva (Alter).	Hemophilia (typical).
0.072	0.047	0.068
0.068	0.056	0.069
0.074	0.058	.....
0.066	0.058	.....
0.071	*0.062	.....
0.073	*0.064	.....
0.062	.....	.....
0.068	.....	.....
0.075	.....	.....
0.069	.....	.....
0.075	.....	.....
0.065	.....	.....

*Calcium lactate (2 gm.) had been given for the previous three days by mouth.

Although there is necessarily a certain degree of error associated with the examination of such a small quantity of blood, yet a comparison of the calcium content of this blood with that of normal and of typical hemophilic cases shows a difference quite beyond the range of error. The first examination of Alter, when he was in the poorest general condition, is most striking in this respect. It will be noted that the calcium increased when lime was given for a few days by mouth. At the time of this increase of blood calcium, the addition of calcium solution to the blood *in vitro* was no longer able to compass a hastening of coagulation. At another time calcium was given in daily doses of 2 grams for over a month, with the result that the coagulation-time was shortened. However, it never reached the normal, nor did the tendency to hemorrhage absolutely cease, proving that a calcium deficiency was not the sole pathological factor in this case. An increase of antithrombin was not present to account for the hemorrhagic condition. A quantitative antithrombin test of this plasma may be found reproduced elsewhere in connection with the description of a new test for antithrombin.[6]

Metabolism Study by Dr. Max Kahn.

We were fortunate in being able to enlarge the scope of our investigation of this case (Alter) by a metabolism study, which, naturally, had as its primary object the determination of the calcium balance. At the same time a similar study was made of another child suffering from hemophilia, a boy of nine years (Julius) who, with his brother, had been under our observation for about two years. This boy was a typical example of hereditary hemophilia, so that the results in these two cases allow us to judge of the chemical processes not only in this atypical case but also in classical hemophilia. As far as we are aware there are no data of similar studies in this disorder to furnish a comparison.

Both patients were fed on a diet of milk, eggs, butter and bread. Duplicate samples of each substance given the patients were sent daily to the laboratory, where they were weighed and analyzed. The urine and the feces were collected daily for examination.

The experiment may be divided into three periods: (1) a fore-period, of a duration of three days, during which time the patients were kept in bed and fed the diet above mentioned, without being given any medication; (2) a calcium-feeding period, also lasting for three days, from August 19th to 22d, 1914 (during this time the patients received daily two grams of calcium chloride and one gram of magnesium oxide); (3) an after-period, lasting three days, during which time there was again no medication. The feces were demarcated, period from period, by means of carmine.

In the analysis of the food the following methods were employed. Nitrogen by the Kjeldahl method; total sulphur by the Wolff and Osterberg method, a modification of the Benedict method; calcium and magnesium by the McCrudden method, after ashing and extracting the ash with hydrochloric acid; phosphorus by the Neumann method.

In the urinary analysis, in addition, ammonia was determined by the Folin method, urea by the Benedict method and the total and ethereal sulphates by the Folin method. The inorganic sulphates were computed by subtracting the ethereal sulphates from the total sulphates, and the neutral by substracting the total sulphate sulphur from the total sulphur. Total phosphorus was determined by the Neumann method, the phosphorus being weighed as magnesium pyrophosphate; creatine and creatinine by the Folin method; and uric acid by the Krueger-Schmidt method. For the feces the same methods were used. In the case of the fat the Kumagawa and Sato method was employed.

The results of the examinations are summarized in the four accompanying tables. (Tables 4, 5, 6, 7.) These show that

TABLE 4.—SUMMARY OF METABOLISM DURING THE THREE PERIODS.

A. TYPICAL HEMOPHILIA (JULIUS).

Substance.	Fore-period (average per diem).				Feeding-period (average per diem).				After-period (average per diem).			
	Food.	Urine.	Feces.	Bal.	Food.	Urine.	Feces.	Bal.	Food.	Urine.	Feces.	Bal.
Nitrogen.....	16.14	10.55	3.75	+1.84	16.10	10.13	2.28	+3.69	14.61	10.38	1.93	+2.30
Sulphur.....	1.90	0.98	0.87	+0.05	1.93	0.91	0.95	+0.07	2.06	0.91	0.95	+0.20
Phosphorus...	3.78	2.13		+1.65	3.26	3.03		+0.23	3.79	2.51		+1.28
Chlorine.....	7.94	6.74		+1.20	9.19	8.17		+1.02	8.58	6.78		+1.80
Calcium.....	1.59	0.206	0.824	**+0.56**	3.39	0.466	2.08	**+0.85**	1.47	0.17	0.71	**+0.59**
Magnesium...	0.51	0.177	0.133	+0.20	1.64	0.84	0.61	+0.19	1.45	0.70	0.53	+0.22

B. HEMOPHILIA CALCIPRIVA (ALTER).

Nitrogen.....	11.53	6.75	2.07	+2.71	11.50	6.99	2.17	+2.54	11.30	7.26	2.78	+1.26
Sulphur.....	1.31	0.88	0.30	+0.13	1.94	1.02	0.33	+0.59	1.84	0.95	0.29	+0.60
Phosphorus..	3.49	2.98		+0.51	3.36	3.09		+0.27	3.91	3.55		+0.36
Chlorine.....	4.60	4.09		+0.51	6.00	5.06		+0.94	5.03	3.44		+1.59
Calcium.....	1.37	0.39	1.80	**−0.82**	3.60	0.73	2.24	**+0.63**	1.33	0.21	0.81	**+0.31**
Magnesium...	0.42	0.19	0.11	+0.12	1.56	0.67	0.32	+0.57	0.67	0.14	0.07	+0.46

TABLE 5.—CALCIUM AND MAGNESIUM METABOLISM (ALTER).

	Day.	CaO. Intake.	CaO. Urine.	CaO. Feces.	CaO. Bal.	MgO. Intake.	MgO. Urine.	MgO. Feces.	MgO. Bal.
Per'd 1.	1	1.35	0.37	1.73	**−0.75**	0.35	0.14	0.09	+0.12
	2	1.40	0.43	1.94	**−0.97**	0.47	0.21	0.12	+0.14
	3	1.37	0.39	1.71	**−0.72**	0.45	0.21	0.14	+0.10
Per'd 2.	4	3.55	0.72	2.31	**+0.52**	1.92	1.21	0.56	+0.15
	5	3.62	0.73	2.14	**+0.75**	1.35	0.42	0.21	+0.72
	6	3.65	0.75	2.28	**+0.62**	1.41	0.37	0.20	+0.84
Per'd 3.	7	1.32	0.12	0.46	**+0.74**	0.87	0.16	0.09	+0.62
	8	0.27	0.24	0.88	**+0.15**	0.62	0.10	0.05	+0.47
	9	1.42	0.27	1.11	**+0.04**	0.54	0.17	0.09	+0.28

During Period 2, calcium and magnesium were added to the food.

TABLE 6.—URINARY NITROGEN PARTITION.

A. HEMOPHILIA CALCIPRIVA (ALTER).

Day.	Amount cc.	Total N. gm.	Urea % Total N.	Ammonia % Total N.	Creatinin % Total N.	Uric Acid % Total N.
1	750	10.56	82.7	4.2	3.1	2.25
2	720	9.87	83.4	4.4	3.4	1.98
3	810	11.23	82.5	3.9	2.9	2.72
4	690	10.07	82.9	3.9	3.2	2.15
5	760	10.11	82.7	4.1	3.1	2.22
6	770	10.27	83.2	4.3	3.2	2.14
7	840	9.87	83.5	3.8	3.4	2.07
8	720	10.56	81.9	4.4	3.3	2.24
9	730	10.72	82.8	4.2	3.4	2.05

B. TYPICAL HEMOPHILIA (JULIUS).

1	450	6.78	82.7	4.2	3.5	1.2
2	530	7.18	83.8	4.4	3.4	1.4
3	470	6.27	83.6	3.9	3.7	1.4
4	490	6.86	85.2	4.3	3.4	1.3
5	520	7.02	82.9	4.4	3.1	1.5
6	580	7.10	84.4	4.1	3.6	1.2
7	620	—	—	—	—	—
8	490	—	—	—	—	—
9	510	7.26	82.8	4.2	3.5	1.2

TABLE 7.—SULPHUR OUTPUT IN URINE AND FECES.

A. HEMOPHILIA CALCIPRIVA (ALTER).

Day.	Urine. Total S. gm.	Urine. Ethereal SO_4 % Total S.	Urine. Inorganic SO_4 % Total S.	Urine. Neutral % Total S.	Feces. Total S. gm.
1	0.82	12.6	72.9	14.5	0.27
2	0.97	14.2	70.1	15.7	0.32
3	0.85	13.7	72.0	14.3	0.31
4	0.89	12.9	69.9	17.2	0.38
5	1.02	12.4	75.0	12.6	0.29
6	1.15	12.2	74.7	13.1	0.33
7	—	—	—	—	0.27
8	—	—	—	—	0.28
9	0.95	13.4	71.1	15.5	0.31
Average	0.95	13.0	72.2	14.7	0.31

B. TYPICAL HEMOPHILIA (JULIUS).

1	0.97	14.3	68.1	17.6	—
2	0.92	14.5	69.2	16.3	—
3	1.05	16.2	65.7	18.1	0.87
4	0.97	12.9	67.9	19.2	0.98
5	0.86	16.1	68.4	18.5	0.85
6	0.89	14.4	68.0	17.6	1.04
7	0.87	14.7	69.0	16.3	0.95
8	0.91	13.8	70.6	18.6	0.90
9	0.94	13.2	69.2	17.6	1.02
Average	0.93	14.3	68.3	17.3	0.94

the disturbances of nutrition are not at all similar in the two children. In both, however, the nitrogen metabolism, the sulphur, and phosphorus partitions and determinations, appeared to be normal. A positive balance is observed in every instance and the output of the various fractions fall within normal limits. The chloride and the fat exchange also seemed undisturbed.

When we turn to the mineral metabolism we find radical abnormalities in the case of Alter, whereas the exchange of lime in the boy with typical hemophilia appears to be normal (Tables 4 and 5). It will be observed from the summary given in Table 5 that the calcium balance of Alter was negative, and that it promptly became positive when lime was added to the diet; in the after-period the retention of lime became increasingly less day by day.

GENERAL CONCLUSIONS.

Typical hereditary hemophilia is not associated with a deficiency of calcium. Our investigations showed, as had others previously, that the addition of calcium to the blood *in vitro* delays rather than hastens coagulation. Furthermore, a deficiency could not be established by quantitative determinations of the calcium in the blood, and a metabolism study showed that the exchange of lime salts, as well as of numerous other inorganic as well as organic substances, differed in no way from normal.

Hemophilia, however, does not seem to be a sharply circumscribed entity, if we group under hemophilia disorders characterized by the three main criteria of this disease: delayed clotting of the blood, a normal number of platelets, and a negative "capillary resistance test." If we demand that the

defect be hereditary, it is possible that no variation in type will be found. The atypical instance which we have studied was of the sporadic variety, but had all the other symptoms of classical hemophilia and therefore cannot be considered as a case of purpura. This boy showed a definite deficiency in the calcium of the blood from a functional point of view, the addition of a weak solution of calcium markedly hastened the clotting of the blood. Quantitative determinations of blood calcium also showed a deficiency compared with the normal. In addition, a study of his general metabolism brought out the fact that there was a negative balance of lime, which became positive when lime salts were added to the diet. Although we do not wish to make the conception of hemophilia more complex, or to burden its nomenclature, it would seem that this instance must be considered a distinctive type of this disorder, an instance of calcium deficiency or a *hemophilia calcipriva*.

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BACTERIOLOGICAL RESULTS IN CHRONIC LEUKÆMIA AND IN PSEUDOLEUKÆMIA.[1]

By C. H. Bunting, Madison, Wis., and J. L. Yates, Milwaukee, Wis.

In a recent article Simon and Judd (Jour. Amer. Med. Asso., 1915, LXIV, 1630) report the cultivation of a diphtheroid organism similar to that found in Hodgkin's disease from the lymph-glands of a case of acute leukæmia, confirming the findings of Steele in a similar case (Boston Med. and Surg. Jour., 1914, CLXX, 123). Although the authors make no strong claim for the etiological significance of their finding, they suggest that the occurrence of the same organism in two cases must be more than fortuitous and emphasize the necessity of further investigations in this group of diseases.

It is with this in mind that we desire to report our bacteriological investigation of two recent cases. The first of these was a case of chronic lymphatic leukæmia of two years' duration, seen by the courtesy of Dr. A. W. Gray, of Milwaukee; and the second was a case of acute lymphosarcoma (or pseudoleukæmia) referred by the Jackson Clinic, of Madison, Wis.

Dr. Gray has kindly furnished the following clinical notes of the first case:

Jan. 18, 1913. W. H. M., male, white; traveling salesman; aged 40.

Family History.—Negative.

Past History.—Childhood diseases and frequent attacks of tonsillitis; tonsils always large. The laryngologist at the Mayo Clinic removed adenoids two years ago. The patient cannot remember whether or not the glands in the neck were enlarged at the time the tonsils were removed, in fact he had not noticed the enlargement until his attention was called to it during the examination.

Present Condition.—Cold in the head, deafness and aphonia.

Examination.—Fairly well nourished, weight 140 pounds. Heart and lungs negative; spleen palpable; pharynx, fauces and vault of mouth show a peculiar red color which does not suggest acute inflammation; granular pharyngitis marked; fragments of tonsillar tissue present; faucial tonsil large; cervical, axillary and inguinal glands markedly enlarged, especially the anterior cervical, many of which were about the size of a hazel-nut. The blood examination showed the leucocyte count to be 186,000. A differential count was not made at this time. Hæmoglobin, 85% (Sahli).

The patient was under active treatment from February 1, 1913, when the leucocyte count was 175,200. He was given benzol in varying doses. Roentgen-ray radiation was given by Dr. O. H. Foerster. The leucocyte count, on March 29, 1913, had dropped to 8200. Sodium cacodylate, gr. ¾, hypodermically, was given at this time once in two days for two or three weeks. There was a decided subsidence of the glandular enlargements during this period, and an almost complete disappearance of the posterior and anterior cervical glands followed the removal of adenoids by Dr. H. B. Hitz on June 26, 1913. Roentgen-ray treatments, benzol and sodium cacodylate have been given as seemed indicated. In general the patient's condition has remained fair during the two years that he has remained under observation. His principal complaint during this time has been lack of endurance and a feeling of weakness, but he has continued at his work whenever active treatments did not interfere. At times he has complained of pleuritic-like pains through the chest which either subsided without special treatment or seemed to disappear after X-ray treatment.

The following counts have been made in his case:

Date.	W. b. c.	Neutr. %	Eos. %	Bas. %	S. Lymph. %	L. Mono. %	Trans. %
II–18–13.....	175,000	48.8	0.0	1.2	7.5	32.5	10.0
III–29–13.....	8,000	66.0	0.0	0.0	5.4	20.6	8.0
IV–17–13.....	6,200	94.5	1.0	0.0	2.0	1.5	1.0
V–24–13.....	6,200	40.0	1.0	0.0	56.5	2.0	0.5
VI– 3–13.....	6,200	41.5	0.5	0.0	48.5	8.0	1.5
VII–21–13.....	7,080	28.0	0.67	0.0	50.7	19.3	1.33
VIII–25–13.....	10,000	26.0	1.33	0.0	44.0	27.0	1.67
IX–22–13.....	10,100	20.0	1.5	0.0	35.0	40.0	3.5
X–13–13.....	15,000	23.0	3.0	0.0	43.0	29.0	2.0
X–23–13.....	6,800	35.1	1.3	0.0	56.0	2.6	4.0
XI–25–13.....	8,800	14.5	0.4	0.0	82.3	1.0	1.8
IV–20–14.....	21,200	15.75	0.75	0.0	81.75	0.5	1.25
V– 7–14.....	15,600	16.0	3.0	0.0	74.0	1.0	6.0
VII– 7–14.....	13,100	15.0	0.5	0.0	81.5	2.5	0.5
IX–18–14.....	14,800	13.0	1.0	0.0	61.0	2.0	23.0
XII–30–14.....	25,500	5.5	0.5	0.0	90.0	0.5	3.5
I– 1–15.....	41,000	3.0	0.0	0.0	96.0	0.0	1.0
III– 2–15.....	63,200	3.5	0.0	0.0	55.0	41.5	0.0
III–31–15.....	92,900	....	....	....	....	....	....
IV–16–15.....	99,400	....	....	....	....	....	....
IV–26–15.....	161,200	....	....	....	....	....	....
V– 8–15.....	92,000	....	....	....	....	....	....
V–19–15.....	65,400	....	....	....	....	....	....

[1] This work has been aided by a grant from the Rockefeller Institute for Medical Research.

Blood smears from this case examined on March 5, 1915, when the leucocyte count was 60,000, showed 3% of polymorphonuclear neutrophiles and 97% lymphocytes, of which 11% might be classified as large lymphocytes. On March 25 a group of glands was removed from the left axilla under the strictest aseptic precautions. The group was thoroughly flamed in a Bunsen burner and then incised and portions of the tissue were planted upon a variety of media, chiefly blood-serum and egg-medium. Some of the tubes thus planted were incubated aërobically, some anaërobically and still others under paraffin seal.

Of these inoculations six tubes remained sterile; four tubes showed a white coccus, one a white coccus and a diphtheroid organism, and one tube a pure culture of a diphtheroid organism, which grew apparently only upon the gland substance itself. By gradual transfers of gland substance, this diphtheroid was finally induced to grow upon Loeffler blood-serum, although at the time of writing it does not grow confluently, but as minute discrete colonies of a glistening whitish appearance. In stained smears it appears chiefly as a banded organism with marked tendency to the development of the clubbed forms. Coccoid forms are present, but the bacillary forms predominate. Morphologically it is identical with the strains isolated from cases of Hodgkin's disease. In its difficulty of cultivation upon artificial media, it resembles closely an organism grown by us from a case we designated "chloroma" because of greenish orbital tumors in addition to general glandular enlargement. Histologically the glands of the two cases are of almost identical appearance in their loss of architecture and diffuse infiltration with small lymphoid cells.

The second case studied presented clinically the appearance of a case of acute leukæmia, in the character of the mouth lesions, in the enlargement of certain cervical glands, and in the presence of cutaneous and subcutaneous tumors. However, blood counts during April and May have shown a leukopenia (5000-6000) with the following differential picture:

	Neut. %	Eos. %	Bas. %	Lymphocytes %	Trans. %
April 15, 1915, 6000..	70.5	0.5	1.0	21.0	7.0
May 17, 1915, 5000..	63.5	1.5	0.5	25.0	9.5
May 22, 1915, 5600..	76.0	0.5	0.5	17.5	5.5

The history of the case is as follows:

April 14, 1915. A. K., aet. 52. Farmer.

Complaint.—Glandular enlargements in neck and groins.

Family and Past History.—Unimportant.

Present Illness.—Eight months ago after extraction of an ulcerated tooth he noted beginning enlargements in the glands beneath the jaw, which progressed and extended to the other side of the neck and to both groins. Later there appeared cutaneous and subcutaneous nodules, some becoming dark in color. Four months ago the gums began to hypertrophy sufficiently to override the teeth.

He has continued to work, but has noted dyspnœa and palpitation after continued exertion.

Physical Examination.—A well nourished, muscular man, of good color. Skin soft and moist. There is a very extensive general lymphatic glandular enlargement with an involvement of the subcutaneous tissue leading to skin changes.

Lymphatic Glands.—Both triangles on both sides of the neck are quite completely filled with nodules varying in size from a cherry-pit to a walnut. In the lower parts these enlarged glands are discrete and movable; above they are matted together and fixed to the surrounding structures, particularly in the submaxillary region, where they seem to be almost subperiosteal. A few have become attached to the skin. Supra-orbital and pre-auricular enlargements are absent. Chains of glands can be felt extending downward on either side of the spine from the suboccipital region.

The left tonsil is distinctly hypertrophic. The submucous adenoid tissue, particularly on the left side, is so enlarged as to make the articulating surfaces of the teeth sink below the level of the gums. There is no distinct glandular enlargement at the base of the tongue. Marked pyorrhœa, caries and dribbling of saliva are present.

Both axillæ contain a few large glands and extending from these downward on to the sides of the chest and forward and upward in front of the pectoral muscles are chains of glands. These are attached deeply and the overlying skin is freely movable, giving an impression that the lymphatics leading into the thorax have been involved, though substernal distress is not manifest, nor are the superficial veins dilated.

Both brachial chains are enlarged above the epitrochlears. The inguinals are considerably enlarged but discrete and movable. Some glands above Poupart's ligament are palpable.

The liver and spleen are both impalpable and neither show enlargement on percussion. No ascites is detected.

The skin involvement is wide-spread from the forehead to the middle of the legs. These lesions seem to be of the progressive type, starting as subepithelial nodules, not tender or discolored. The epithelium wrinkles over these early nodules and when they are depressed assumes a pigskin appearance. Later reddening occurs and finally a dull purplish color develops. Now the epithelium has become adherent and looks like grain-leather. At times regression occurs in these nodules, leaving behind a macular-like discoloration. Ulceration has not occurred; no itching nor discomfort other than mechanical has been noted.

On April 15 Dr. R. H. Jackson excised a cutaneous nodule for culture and for histological examination. The cultures from this nodule resulted in the growth of a white coccus in three tubes and of a slow-growing diphtheroid and a rapid-growing coccus in a fourth. An attempt to isolate the diphtheroid failed.

On May 22 a second skin nodule was excised. The skin surface was seared in a Bunsen flame and the tissue dissected off from the under side of the nodule for culture.

This second attempt resulted in the growth of a diphtheroid in four tubes, a coccus in one, and no growth in five tubes. The organism is morphologically like that found in the previous case, yet grows somewhat more freely upon artificial media. Its cultural characteristics have not yet been determined.

Histologically the skin nodule shows a diffuse infiltration, of the corium and subcutaneous tissue, by cells of the large mononuclear type, similar to those seen in the blood in acute leukæmia and those found in the lesions of lymphosarcoma. As in lymphosarcoma there appears to be no destruction of the infiltrated tissue. There is a slight fibroblastic stimulation.

The etiological relationship of this diphtheroid organism to the diseases described must perhaps remain for a time *sub judice*. The occurrence of similar organisms in a variety of diseases would certainly seem to be an argument against their etiological importance. However, it is our experience thus far that this type of organism is found with readiness only in one general group of apparently related diseases and in these without fail with good technique. In this group we would include Hodgkin's disease, the lymphogenous leukæmias, the pseudoleukæmias (lymphosarcoma), Banti's disease and probably also mycosis fungoides. Outside of this group, if the organism is found, there is also some histological evidence of its activity.

ICONOGRAPHIC NOTES ON GIROLAMO FRACASTORO.[1]

By Arnold C. Klebs, M. D.

The name of Fracastoro appeals with peculiar emphasis to us medical men in the present-day development of our science. Fracastoro's contemporaries saw in him, as we still do, the erudite scholar and elegant poet, the ingenious interpreter of some of nature's secrets (in the heavens as well as on earth), the physician as well as the friend of the highest of his time, a kind helper to the humble and an inspiring teacher of the young. But to us he is still more; his work marks a new era in medicine, the era of bacteriology which has brought about in our generation far-reaching results, not only in our etiologic conceptions, but also in their prophylactic application. It has taken three hundred years to recognize the fundamental significance of Fracastoro's teachings; and when we now read in the transactions of learned societies, in the journals of the sixties, the discussions about the early attempts at correlating certain diseases with the minute organisms then discovered, and note the profound scepticism and even derision with which they were received on all sides, we must wonder, indeed, that similar conceptions could have arisen three centuries ago. And this is exactly what happened in Fracastoro's case. Call it intuition, anticipation, guess-work or what not, the fact remains that his idea had immense potentiality. It makes one realize that ideas of men of genius, however little their significance may be understood at the time, always merit respectful attention—a further plea for the cultivation of historical studies in medicine.

The earliest, most primitive idea, that disease is the result of some harmful agent entering the body from without, was curiously enough not taken up by the school of medicine of more advanced eras. Almost all maladies were explained as internal disharmonies, or the corruption of the fluids and solids composing the body. Only towards the end of the middle ages did the idea of the rôle of infection begin to find advocates. Here Fracastoro made one great step in advance, at least in the light of our present-day conceptions, which we must always guard ourselves from considering as final. He not only insisted on the external origin of certain diseases, but came to the logical conclusion that the foreign bodies, the "seminaria," or seeds, imperceptibly invading the organism, must possess qualities of life and reproduction, and that, therefore, disease produced in this way must become transmissible from the sick to the healthy. He was aware—and stated it with unprecedented clearness—that this transmission could take place by direct contact, through the air or infected objects, the "fomites," an idea which, as I have shown elsewhere,[2] had already been expressed in a verse of the School of Salerno. This idea of an animate contagion we find for the first time painstakingly analysed as to its significance and practical consequence in Fracastoro's work. The various infectious diseases are described and explained on this basis; phthisis, for instance, is for the first time definitely placed among them. What a fund of minute observation and lucid discrimination do we find; for example, in that chapter on the fevers called "lenticular or punecticular," in which we unmistakably recognize the first description of typhus.[3] Fracastoro's *De contagione et contagiosis morbis* (published in Verona in 1546), in which all these advanced conceptions are to be found, undoubtedly marks the beginning of the scientific investigations of infectious diseases. It is of much deeper meaning to us than his other great work upon which rests his wider fame among his contemporaries.

This work, a poem, in form modelled after the Georgics of Virgil, in substance treating of that strange disease which from the time of the French siege of Naples, under the name *morbus gallicus*, or *mal franzoso*, attracted the keenest and most interested attention of Fracastoro's contemporaries. To us this poem is interesting, chiefly because its hero, the shepherd *Syphilus*, has given his unprejudicial name to this malady for times to come. Fracastoro has left us other contributions, bearing the imprint of far-seeing genius. They have, not long ago, been discussed and analyzed most charmingly by Dr. Osler, so that our passing allusion to his greatest work may here suffice.

Of the external circumstances of Fracastoro's long life (1483-1553), we also possess several excellent accounts. Born in Verona, he belonged to a distinguished patrician family. Even in the 13th century one of his ancestors, Aventino, had attained fame as the physician of Can Grande I, that mighty condottiere and patron of the arts and letters, as testified by his friend Dante. Little known is the handsome canopied tomb of this Fracastoro on the façade of S. Fermo Maggiore, before which our Girolamo surely had often passed. Up to 1508 we find Fracastoro studying and teaching at the University of Padua, which was closed in that year because of war. Later he passes through Pordenone, and finally settles near Verona on his farm at the foot of Monte Baldo, whence he could overlook Lake Garda and Catullus' Sirmio and the towers of his native town rising out of the wide, fertile Lombard plain. As a true Cinquecento scholar his interests were manifold and by no means confined to medicine. He was at home in mathematics, astronomy, geology, philosophy; enjoyed and cultivated poetry and music. In our time of specialism, such universal proficiency is difficult to comprehend, but among learned men of that day it was rather the rule than the exception. Fracastoro, himself, as also his biographers, gives us the names of his numerous friends and associates. Many of the best of his time are among them. Among physicians we know of his close association with the dalla Torre family, also from Verona; the father, Girolamo,

[1] Read before the Medical and Chirurgical Faculty of Maryland, Baltimore, June 16, 1915.

[2] The Johns Hopkins Hosp. Bull., 1913, XXIV, 70.

[3] Imported from Cyprus and the neighboring isles into Italy in the years 1505 and 1528.

was his teacher in practical medicine in Padua, and intimate friendship bound him also to the younger dalla Torre, Marc Antonio, the friend and anatomical co-worker of Leonardo da Vinci. Others were G. Cesare Scaliger, Gianbattista Montanus, Aloisio Mundella, to mention only a few. Whether his practice as a physician was very extensive we do not know, but undoubtedly he gained much experience in several of the epidemics which ravaged Italy, and on the battlefields in the Venetian army under Bartolomeo Lavinio. Among his many prominent patients we know of Pope Paul III and Caterina de'Medici.

Fracastoro's earliest biographer, an anonymous author, probably a contemporary, gives a description of his external appearance: "Of low though sturdy build, broad shouldered, with handsome beard, black, abundant hair, round face, dark eyes, the nose short and turned upwards by his frequent contemplation of the stars; serenity and ingenuity of mind mirrored in his features." Mencken, to whom we owe the most extensive biography of Fracastoro, adopts this description in general, but does not fail to see the absurdity of the peculiar deformation of the nose and its cause. "Woe unto ye astronomers," he exclaims, "if the stars thus endanger your noses"! This description, we may safely conclude, gives us but scant and not very reliable information on the subject. We must, therefore, turn to extant portraits. A great number exist, but for us only those can be of interest which were most probably made from life. Upon careful examination, we find that the majority were done after Fracastoro's death from the very few likenesses we know to have been made during his lifetime. I have searched in Verona and Padua for a contemporary painting of him which was said to exist, but I have been unable to find anything that could be identified with certainty. In the Museo Civico in Verona two canvases were pointed out to me as possibly representing Fracastoro. One is in a group, by Turbido: an old man with white hair and beard sitting in the foreground is evidently painted as a portrait. The painting is in very bad condition and cannot be used for identification without better information about its origin, which is shrouded in complete mystery. The other is a portrait, attributed to Titian, of a man between 50 and 60 years of age. It depicts a forceful man of action, a statesman or great noble, rather than a contemplative scholar. A golden chain around his neck also speaks for this view. If we put these two paintings aside as very doubtful likenesses of Fracastoro, there remains, as far as I know, only one engraving, a wood-cut, which represents him as he really was. It appears as frontispiece to Fracastoro's astronomical work "de Homocentricis," which was published in Verona in 1538. This portrait has evidently served as prototype for the swarm of likeneses which appeared later. An excellent reproduction of this portrait is given in Garrison's "Introduction to the History of Medicine" (Philadelphia, 1914), so that it is not necessary to repeat it here. Fracastoro, at the time of the publication of this work in or near Verona, was about 50 years old, and it seems very probable that he sat for the frontispiece destined for his book. We do not know the artist, but this portrait speaks for his mastery of technique. Without hesitation and apparent attempt at idealization, he has drawn a strong, realistic likeness. The dark eyes, rather far apart and deep-seated, looking out into the distance, the slightly curved nose with a small wart on the right side, the firmly closed mouth and straight lower lip, the square form of face with prominent cheekbones, the broad, slightly receding forehead and skull discernible under the abundant long hair of head and beard, all that we feel the artist drew as he saw it before him. The pose is three-quarter face and Fracastoro wears a three-horned biretta, a wide-sleeved coat with fur collar, ruffled cuff, and in his right hand, of which the index finger carries a ring with a large oval stone or seal, he holds an armillary sphere and a laurel sprig, insignia which have been usually repeated in the later reproductions.

There are two other contemporary portraits of Fracastoro which are undoubtedly intended to represent him. They are bas-reliefs showing him in profile and, I believe, are both inspired by the drawing of the wood-cut just described, although I am unable to prove this conclusively. The more important is a large medallion in bronze which was made about 1551 by Giovanni Cavino,[4] the renowned medallist of Padua, on the order of Gianbattista Ramusio, then Secretary of the City Council, and placed with a similar medallion, also by Cavino, of Fracastoro's and Ramusio's friend, Andrea Navagero, at the Porta San Benedetto in Padua. This medallion is now in the Museo Civico of Padua, where I have examined and photographed it. It gives only the relief of the head in profile, surrounded by the name. The modelling is good, but bears the stamp of conventionality and idealization. It does not bring out any salient, characteristic features. The head is uncovered, showing the shape of the skull. It may be held that it represents an older man than the wood-cut, more nearly the age of 67, which Fracastoro had about reached when this work was executed and that, therefore, Fracastoro might well have posed for it. For various reasons, which it would take too long to enumerate, I believe that this relief is nothing more than a conventional representation of Fracastoro, and not an authentic likeness. The same, I believe, is equally true of the second profile, also in bronze on a smaller medal, attributed to Giulio dalla Torre (a learned professor of the law in Padua, and younger brother of Marc Antonio). This medal may not be genuine at all, as some (*e. g.* Friedlaender) think; at any rate it is a charming piece of work, though more likely taken from the wood-cut than from life. Neither one of these reliefs, therefore, helps us to visualize clearly Fracastoro's features.

Well known, perhaps better than any of the portraits described, is the Fracastoro statue in Verona. Standing on the Piazza dei Signori, with his back against the Palazzo della Ragione, one faces the statue of Dante, and behind it rises the charming Renaissance building, the Palazzo del Consiglio, adorned with the statues of five famous Veronese, the younger

[4] Cavino was also a very clever imitator of the medals representing Roman Emperors, a fact which has given much trouble to modern numismatists.

Pliny, Cornelius Nepos, Macer, Catullus and Vitruvius. It adjoins a narrow street, over which spans a graceful stone arch. Upon this, high up on a pedestal, too high for close examination, is placed this marble statue of Fracastoro. The pedestal bears the legend:

HIER · FRACASTORIO ·
PAVLLI · PHILIPPI · F ·
EX · PVBLICA · AVCTORITATE ·
DICATA
AN · SAL · MDLIX ·

The artist has represented Fracastoro erect, above life size, draped in a long, antique toga, the head slightly inclined forward and to the left, the right arm bent at a right angle, the hand holding a globe, the left arm hanging at his side. The features seem to belong to a man older than the one in the wood-cut; the full beard and the hair of the head are more abundant than in the other portraits. Otherwise there is an unmistakable similarity of feature, especially to those of the Cavino head. The decree of the Senate which provided for the erection of this statue is dated 1555, and it seems that in that year it was put up somewhere in the Piazza d'Erbe, to be transferred later, possibly in 1559, the date of the epigraph, to the place it now occupies. The documents mention as the artist of this statue: "*Danesium Cataneum Carrariensem ex Lunense agro.*"

An interesting feature of this statue is that the artist who carved it seems to have also done the bronze bust of which a reproduction is here given. So far as I am aware, it has not appeared in medical publications. Danese Cataneo was sculptor, architect and poet, a pupil of the famous Sansovino and closely connected with that group of men which Fracastoro frequented and among whom Tasso was his close friend. We find many fine examples of his work in the Venetian provinces. It is characterized by certain distinct features of realistic treatment which aid in its identification. The bronze bust before us, since 1827 in the Imperial Museum of Vienna, has only recently been recognized as Cataneo's work. For a long time it stood in the museum, not much noticed, as the work of an anonymous artist, after which it was for a time thought to have come from the studio of Alessandro Vittorio, until finally more painstaking comparisons and a scientific study led to the present attribution. The assertion that the bust represents Fracastoro was made to the museum authorities by the dealer in antiquities, a Roman, Giacomini by name, who also stated that he had bought it is as such in Verona. There is no inscription or other document to strengthen this tradition.

In comparing the features of this bust with any of the others of Fracastoro, one is immediately struck by some obvious differences, so much so that one is inclined to dismiss any consideration of their representing the same person. We have always seen Fracastoro with a beard. On the bronze head we see only the rough, unshaven chin and upper lip, the head cropped, not shaved; and as we examine the features, involuntarily we recall the Hippocratic facies: "a sharp nose, hollow eyes, collapsed temples; the ears cold, contracted and their lobes turned out; the skin about the forehead rough, distended and parched . . . ." The majesty of death hovers over this face, striking and repellent. Could it perhaps be that the artist has made a death mask from the dead Fracastoro, worked it over slightly in certain parts, the eyes, for instance, adding the bust portions to it, as a preliminary study for the statue which the Senate had ordered of him? It is obvious that these questions cannot be answered positively, but we do know that such a procedure was not uncommon among the artists of that time, who strove for most realistic representation. From this very striving came, in great measure, the impetus which anatomy received in those days. Of Verrocchio, for instance, we know that he used plaster casts of any part of the human body for models in his work, and masks from the living as well as from the dead were still more frequently employed in this way. An exact comparison of the head of this bust with that of the statue alone might decide what there is to this conjecture. It is natural that Cataneo would have tried to remove in the statue the characteristic features of the death mask and add, of course, the beard, which may have been clipped off for the taking of the mask. Probably while making such modifications the artist would have preserved the general proportions, especially those of the bony parts of skull and face. An exact comparison may be possible, although several attempts to obtain good pictures of the head of the statue have so far failed on account of its elevated and inaccessible position. Until such a comparison decides the question one way or the other, we may safely assume that the bronze bust represents Fracastoro at a more advanced age than the other portraits. He was seventy years old when he died in 1553, while, as we have seen, he appears as a vigorous man of about fifty in the most authentic representation we possess.

This bronze bust being one of the best examples of Cinquecento sculpture in Vienna, the museum authorities are naturally interested to know whether or not it represents Fracastoro.

In my studies on the subject I have been aided by them in various ways, and my particular thanks are due to Professor Hermann, the learned custodian of the Hofmuseum, as well as to the directors of the civic museums in Padua and Verona, Professor Moschetti and Professor Rizzoli.

This iconographic problem will retain its interest to medical men, no matter what the result of further research may be. This is the only excuse I can offer for presenting my study in an unfinished stage.

JOHNS HOPKINS HOSPITAL BULLETIN.

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BRONZE BUST SAID TO REPRESENT GIROLAMO FRACASTORO, ATTRIBUTED TO DANESE CATANEO (CIRCA 1559). NOW IN THE VIENNA HOFMUSEUM.

AN EXPERIMENTAL STUDY OF THE FACTORS RESPONSIBLE FOR NON-INFECTIOUS BONE ATROPHY.*

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INTRODUCTION.

The purpose of this investigation has been to secure more information of an experimental nature concerning the causes of bone atrophy. The atrophic changes which accompany infectious processes have not been considered here.

The clinical importance of this condition has been recognized for some years, but it is only recently that active measures to combat it have been advocated in the treatment of joint injuries, fractures, etc. Lovett [14] has drawn attention to a series of interesting—occasionally incapacitating—complications, such as varying degrees of ankylosis, articular swelling, pain and increased susceptibility to fatigue which may follow the presence of such an atrophy. He emphasizes the necessity of considering these possible after-results in treating all orthopedic cases, and of instituting appropriate therapy when immobilization plays a prominent part. The occasional occurrence of spontaneous fractures in patients showing an advanced atrophy of the bones emphasizes still more the possible consequences of this condition.

While it appears that the therapeutic test has demonstrated the efficacy of active and passive motion, massage, etc., in combating bone atrophy, we shall not be in a position to use these measures to their best advantage until more is known concerning the factors which are directly responsible for such a complication. Various hypotheses have been advanced from time to time, the oldest perhaps being that such changes are due to the influence of the central or the peripheral nervous system. In this way the descriptive terms "trophic atrophy" and "nervous reflex atrophy" arose. Later an important rôle was ascribed to inactivity. More recently emphasis has been laid upon the nutrition of the part involved, a change in the vascular supply being recognized as the principal factor responsible for immobilization or disuse atrophy.

The series of experiments reported here were undertaken in order to ascertain more definitely, if possible, the relative importance of these several hypotheses.

METHODS EMPLOYED.

The experiments were conducted on thirty-eight rabbits and nine dogs. In both series of animals the bones entering into the formation of the ankle and wrist joints proved to be the most suitable for such a study. Structural changes in the cortex and medulla were followed by means of the Roentgen-rays. The limb opposite the one experimented upon was used as a control. As frequent X-ray examinations were made in each case, it was possible to follow closely the appearance and the progress of atrophic changes.

Where nerves were cut, it was found that wrapping the affected limbs in adhesive plaster protected the skin from superficial and deeper infections. Infected animals were discarded from the series. Throughout the operative procedures the rabbits and dogs were kept thoroughly anæsthetized with ether.

The results from the experimental work are discussed under four principal headings: (1) the nervous influences in bone atrophy; (2) the blood supply in atrophy; (3) inactivity or immobilization in atrophy; (4) immobilization in bone repair. Summaries of the more typical protocols have been included in each of these divisions.

NERVOUS INFLUENCES IN BONE ATROPHY.

EXPERIMENT I.—*Dog No. 4. Laminectomy.*—Resection of a centimeter of the posterior or sensory roots of the lower three lumbar and first sacral spinal nerves, left side. Healing *per primam*. During the first few days of convalescence the left hindfoot appeared weaker than the right. While running, the leg was held above the ground; while walking, loss of sense of position was apparent. On the ninth day the gait appeared practically normal; the animal ran and jumped as freely as before operation. The dog was given ample exercise each day.

Roentgen-ray examinations made at frequent intervals revealed no structural differences in the bones of the two hindlegs, even as late as two and one-half months after the root resections.

EXP. II.—*Dog No. 2. Laminectomy.*—Resection of a centimeter of the anterior motor roots of the last three lumbar and the first sacral spinal nerves, left side. Healing *per primam*. The dog was active on the day following the operation. In walking, running, defecating etc., there was a complete disability of the involved leg. The animal received ample, active exercise each day.

At the end of the fourth week the Roentgen-ray examination showed very slight structural differences between the bones of the hindlegs. Two weeks later (six weeks in all) there were definite signs of beginning atrophy indicated by the disappearance of some of the finer trabecular lines and the presence of small areas of absorption in the cortices of the tibia and fibula. Two months after the operation there was a further advance in the atrophic process—a thinning of the cortical portions of the metatarsal bones. Some slight additional changes were apparent at the expiration of two and one-half months.

EXP. III.—*Dog 5.*—A plaster cast was applied to the left foreleg so as to immobilize it completely. The dog was unable to step on the limb and made no attempts to use the shoulder muscles of this side.

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Structural changes appeared about the fourth week. They were found to advance somewhat more rapidly in this animal than in that of the preceding experiment (Exp. II). About two months after the application of the cast, signs of a moderately advanced atrophy were seen both in the cortex and in the medulla of the bones of the foreleg.

Exp. IV.—*Rabbit No. 13.*—About a centimeter of the left sciatic nerve was excised high in the thigh. The animal was kept in a cage with other rabbits and was active throughout the period of observation. Healing *per primam.*

No difference in the two legs was noticed during the following four weeks. One and one-half months after the operation slight changes were visible: the cortex appeared a little thinned and the trabeculæ, though distinct, were somewhat finer. After two additional weeks the medulla was less dense, and the shadows cast by the bones as a whole were slightly less clear.

Exp. V.—*Rabbit No. 19.*—Small segments of the left anterior crural and the sciatic nerves were excised high in the thigh. Healing *per primam.* Active exercise.

Roentgen-ray examinations showed a beginning atrophy at the end of the second week—the cortex a trifle less compact and structural lines in the medulla somewhat fainter. There was even a possible difference seven or eight days after the operation. Subsequently a slow advance in these changes was noted. A comparison of the roentgenograms made at corresponding intervals after operation from this experiment with those from Exp. VIII showed more atrophy in the latter.

Discussion.—The conception that atrophy of bone is controlled to a greater or lesser extent by nervous influences has occupied men's minds as long as the subject of atrophy has formed a problem for speculation. We find in Petit's [18] *Traité des Maladies des Os* that atrophy is an accident which supervenes not at the beginning, but later, from enfeeblement of nerves and arteries which continue to be compressed, either by exuberant callus or by too tight bandaging.

Schiff,[22] in 1854, cut the sciatic and crural nerves in young dogs and observed first an atrophy and later (12-18 months) a hypertrophy of the bones (entzündliche Knochenneubildung). Nasse [17] and Mantegazza [15] repeated these experiments and rejected all animals showing infections. On the paralyzed side they found a general atrophy of all of the constituents of the limb. This was interpreted as being trophic in origin.

Rasumonsky,[20] from an experimental study in 1884, ascribed a considerable rôle to trophic nerves which, he believed, influenced the circulation of the part. A few years later Wolff [27] expressed much the same view. Schuchardt [23] also emphasized the neurotrophic factor as the most important in the development of bone atrophy. Sudeck [25] accepts Nasse's conclusions and cites cases of atrophy due to peripheral nerve injuries. Sudeck, Kienböck [12] and Exner [6] regard the rapidly appearing forms of atrophy as reflex or trophoneurotic in origin.

Recently Brandes [4] has shown that atrophy may arise from inactivity much sooner than was formerly believed. He considers that the rapidly appearing atrophies are caused by inactivity and not by neurotrophic or reflex influences.

The effect of dividing the posterior or sensory nerves which supply the leg and foot is shown by Experiment I to be minimal. No signs of atrophy were evident in this case as late as two and one-half months after the operation. As the anterior or motor roots were left intact, complications arising from inactivity were obviated.

Experiments IV and V illustrate the effects of destruction of peripheral nerves. A moderate degree of atrophy was observed in both. This probably was an inactivity atrophy due to the paralysis of the muscles. On comparing the degree noted in each of these experiments with that observed in Experiments X and XI, it was found that the changes were more advanced in the latter. As frequent observations of the animals showed that a greater immobilization was produced by the casts than by cutting the nerves, the conclusion is justifiable that the atrophy present in Experiments IV and V was due to inactivity alone. It is thus apparent that peripheral nerves have no direct influence on the production of bone atrophy.

The purpose of Experiment II was to determine whether motor nerves exert any direct trophic influences upon the nutrition of bone. A certain amount of atrophy was noted subsequent to the motor-root resections, but since a comparison of the plates from this experiment with those from Experiment III reveals more advanced changes in the latter, this atrophy may fairly be attributed to inactivity. The dog with the motor root divisions gave the affected limb considerable passive motion; whereas the one with a leg immobilized in plaster held the corresponding shoulder muscles firmly fixed.

In all of the published work which concerns the nervous influences in bone absorption no satisfactory means have been employed to differentiate between the trophic and the disuse factors. Up to Brandes' investigations, moreover, there has been a failure to recognize the early changes which result from inactivity alone. These facts together with the negative nature of the results from the nerve experiments reported here, accordingly, warrant the conclusion that the sensory and the motor nerves of the limbs exert no direct reflex or neurotrophic influences on the development of bone atrophy.

THE BLOOD SUPPLY IN BONE ATROPHY.

Exp. VI.—*Dog No. 3.*—Ligation and division of the right subclavian vein. Healing *per primam.* On the day following the operation a slight puffiness was evident in the affected paw. The dog was nevertheless active, walking and running about the yard as usual.

Roentgen-ray examinations made over a period of two months revealed no structural changes in the bones of the operated leg.

Exp. VII.—*Rabbit No. 5.*—Ligation and division of the femoral and saphenous veins, left hindleg. Healing *per primam.* For a day or two there was a slight fullness of the affected forelimb. The animal used all four legs actively throughout the period of observation.

Roentgen-ray examinations, made at frequent intervals for two and one-half months, showed no changes indicative of atrophy in the operated leg.

Exp. VIII-A.—*Dog No. 6.*—Ligation and division of the ulnar and common interosseous arteries in the right foreleg. Healing *per primam.* The dog was active on all four limbs throughout the weeks of study.

Roentgenograms made at the end of the first week showed no differences in structure between the bones of the two forelegs. Seven days later there were still no definite indications of a beginning atrophy.

Exp. VIII-B.—(Two weeks subsequent to part A.) Ligation and division of the radial artery near its point of origin in same leg (right foreleg). Healing *per primam.* During the following seven or eight days the surface temperature of the affected paw remained

considerably lower than that on the control side. Nevertheless, at the end of this time no appreciable structural differences were found between the bones of the two forelegs. Roentgenograms made at later dates also showed absence of any clearly defined atrophy. It should be mentioned that in this half of the experiment the dog was again given ample exercise each day.

EXP. IX.—*Rabbit No. 4.*—Ligation and division of the right femoral artery high in the groin. Healing *per primam*. The animal continued active subsequent to the operation.

No structural changes were noted up to the sixth week. At this time the shadows cast by the ankle-bones appeared to be slightly less distinct on the affected side. No definite atrophy was noted, however, in either the cortex or the medulla two months after the operation.

Discussion.—Helferich [10] and Schüller [24] have each reported experiments in which they observed an increased bone growth following the establishment of an artificial venous hyperemia. Wichmann [26] and Stoltzner, on the other hand, found an atrophy, occasionally marked, in fractured thigh-bones which were suspended vertically for a considerable time. This they attributed to an arterial and venous anæmia resulting from the elevated position of the limbs.

By means of a thermometer Berginen [2] demonstrated differences between the affected and the normal thighs in numerous cases of hip disease. The atrophy present in these patients he ascribed to an impairment of the nutrition of the parts.

Marked atrophy without immobilization in a class of patients with joint disease Legg [15] believes is due to an interference with the blood supply from pressure on the femoral artery. He considers that the atrophy which results from disuse or functional inactivity is due to changes in the nutrition of the part through vasomotor influences.

In Experiments VI and VII there was sufficient interference with the circulation to cause a transitory edema of the forelegs. As no subsequent changes in the structure of the bones were noted, it appears probable that passive hyperemia in itself brings about very little, if any, atrophic changes. It is to be noted that the complication of inactivity did not enter into these experiments, since the animals had ample exercise each day and used the operated as well as the control foot.

Experiments VIII and IX were carried out in order to ascertain more satisfactorily the significance of disturbances in the arterial blood supply. As the animals were active, using all four feet throughout the periods of Roentgen-ray observation, the bones in the operated limbs were subjected to vascular changes of an anæmic type without being in any way immobilized. The difference in surface temperature noted in Experiment VIII affords evidence that the operations were successful in establishing an anæmia of the affected part. Clinical cases with well-defined disuse atrophy, as a rule, show no such signs of nutritional disturbances. The fact that no definite atrophic changes were discernible in either of these experiments suggests that the atrophy resulting from inactivity is due rather to a diminution or loss of the functional stimulus normal to bone than to vascular changes—*i. e.*, a local anæmia. Should the anæmia be sufficiently marked to seriously affect the viability of the part, an ischemic atrophy of all the tissues would result. The atrophies noted by Legg in patients showing no immobilization may be explained in this manner, though the bacterial toxins present in many cases of hip disease are undoubtedly responsible for some degree of absorption.

Concerning the part played by vasomotor nerves in the blood supply of the limbs, there is still considerable uncertainty. While various physiologists have shown that muscular activity is accompanied by an increase in the blood flow through the muscle, there is still no agreement as to the significance of either vasodilator fibers (Goltz) [8] or of the chemical action of metabolic products, such as lactic acid, etc. (Bayliss) [1]. At present, according to Howell,[11] we may accept the view advocated by Gaskell [7]. The latter holds that the vasomotor supply to the muscles consists essentially of dilator fibers. Whenever the muscles contract these are brought into action, providing a blood supply proportional to the functional activity of the part.

In the absence of further evidence we may accept the same explanation for the regulation of the nutrition of bone. From this, however, it does not necessarily follow that the atrophic changes which muscle and bone undergo when they are immobilized result entirely or in a large measure from the decrease in the local supply of nourishment which accompanies such states of inactivity. A normal limb, if kept at rest, will continue to receive a quantity of blood perfectly adequate for such a physiological state.

In functional hypertrophy the opposite relations probably exist. The parts enlarge, grow, not as a result of an augmented blood supply, but due to the increased demands made upon them. They respond to the additional functional stimuli. The greater vascularity simply keeps pace with the growth, supplying the increased requirements for nourishment.

Since the nerve fibers regulating the vasomotor tone of the extremities must enter the limbs by way of the brachial and lumbar plexuses, Experiments IV and V afford examples of limbs isolated from reflex vasomotor control. In Experiment I, on the other hand, such fibers as may have entered the plexus through the post-ganglionic communications remained intact (see below). Notwithstanding this loss of central control the bones in the affected parts showed no atrophic changes attributable to vasomotor influences.

From the experimental work of Goltz [8] it appears that when the spinal cord is destroyed except in the cervical region there is a paralysis of vascular tone in the posterior extremities. Since this tone may ultimately be restored, the resumption of tonicity must be referred either to the properties of the muscular coats of the arteries themselves, or to the activity of the sympathetic nerve cells that give rise to the post-ganglionic fibers. If we were to assume that the absence of atrophy in the animals cited is due to such a resumption of vascular tone—*i. e.*, to a readjustment of the altered circulation—Experiments IV and V would indicate that this probably results from the activity of the muscular coats of the arteries themselves, for the post-ganglionic fibers were severed in the divisions of the sciatic and anterior crural nerves.

While it is conceivable that a re-establishment of the vascular equilibrium may take place through the activity of the arteries themselves, it appears unlikely that the changes in nutrition,

which such a resumption of vascular tone is capable of effecting, are sufficiently marked to account for the absence of bone atrophy in these animals. This view is borne out by the results from Experiments VIII and IX. In the latter experiments a very definite local anæmia was produced; nevertheless, no atrophic changes were noted in the parts affected.

INACTIVITY IN BONE ATROPHY.

Exp. X.—*Rabbit No. 6.*—Plaster cast applied to right hindleg so as to immobilize the joints in the usual sitting posture.

Roentgenograms made on the fourth day of fixation showed that the trabecula within the calcaneus of the affected limb were less distinct than on the control side. All of the finer lines were visible, however. At the end of the first week these changes had advanced so that there was a rarefaction of the distal ends of the tibia, calcaneus and the other tarsal bones. This was marked in the posterior end of the calcaneus. The outlines of the cortex were hazy. The crest of the tibia was indistinct, especially near the internal malleolus. Two weeks following the immobilization the cortices of the distal end of the tibia and of the tarsal bones were definitely thinned. The shadows cast by the trabeculæ now appeared more indistinct and delicate. At the end of two months the structural changes were marked. Near the epiphyseal line at the lower end of the tibia the usual markings were largely absent. There was rarefaction, especially advanced in the posterior portion of the calcaneus, and fewer lines were present in the medulla. The cortices of even the metatarsal bones were now greatly thinned. A comparison of the roentgenograms (made at corresponding intervals after operation) from this experiment with those from Exps. IV and V, shows a more advanced atrophy in the former.

Exp. XI.—*Rabbit No. 28.*—A plaster cast was applied to the right hindleg—fixed in the completely extended position. The arrangement embarrassed the animal in walking about its cage and afforded a very effective fixation of the part.

Changes in the finer architecture and in bone density appeared about the fourth day, as in Exp. X. In later examinations, however, the atrophy was found to advance somewhat more rapidly in the former.

Exp. XII.—*Rabbit No. 26.*—Tendo achillis cut in right hindleg. Healing *per primam*. The animal was active on its three normal feet on the following day.

One week later roentgenograms showed definite atrophic changes. A rarefaction of the distal end of the tibia and of the tarsal bones was visible, particularly in the posterior end of the calcaneus. The outlines appeared softened and the trabeculæ somewhat indistinct. The cortex of the tibia near its anterior margin was especially hazy. Two weeks more disclosed a thinning of the cortices of the lower tibia and the tarsus and a loss of numerous trabeculæ within the bones. The remaining medullary shadows were more delicate than formerly. As compared with the changes noted in Exp. X at the expiration of two weeks the findings here showed more structural modifications (thinning of the cortex and loss of the trabeculæ) but less general rarefaction (decrease in the intensity of the shadows cast by the bones). During the subsequent four months there were signs of a progressively increasing atrophy. The last roentgenograms showed a rather striking difference between the two sides: the cortices of the tarsus and metatarsus were much thinned, the finer structural lines were very faint or absent especially in the calcaneus, and the bones, as a whole, appeared much rarefied.

Exp. XIII.—*Rabbit No. 11.*—Tendo achillis cut in right hindleg. Posterior tibial artery ligated and divided high in the calf. Healing *per primam*.

Subsequent roentgenogram studies showed changes corresponding to those noted in the previous experiment (Exp. XII). The division of the artery apparently did not hasten the atrophic process.

Exp. XIV.—*Rabbit No. 20.*—Small segment of sciatic nerve resected high in the right thigh. Right hindleg immobilized in plaster. Healing *per primam*.

Two weeks later practically the same changes were found here as were noted in Exp. X. In roentgenograms taken subsequent to this period, the progression of the atrophy corresponded very closely to that observed in the latter experiment.

Discussion.—The fact that inactivity may lead to atrophic changes in the affected bones has been recognized for many years. During this period, however, there has been a great difference of opinion concerning the relative importance of inactivity as compared with neurotrophic influences and vascular changes.

The conclusion drawn by Brackett [3] from a clinical study was that functional inactivity may alone account for the atrophy seen in joint disease.

Sudeck,[25] Kienböck [12] and Exner,[6] while recognizing a true disuse atrophy, taught that it is of very slow onset. In rare instances Sudeck found changes as early as six to eight weeks following a fracture.

The recent investigations of Brandes [4] have afforded a new conception of the part played by immobilization. Even where the loss of function in a part is only partial, an inactivity atrophy may soon appear. The greater the inactivity, moreover, the more intense are the atrophic changes.

These observations are consistent with the histological findings of Roux,[21] who showed that not only do certain trabeculæ of the medulla atrophy or disappear when trauma or a change of function establishes a new adjustment of the lines of force in the bone, but that a compensatory hypertrophy may occur in trabeculæ, and new ones may even appear. In other words, he found a very striking physiological adaptation of the structure of a bone to its function.

The results from Experiments X, XI and XII confirm the findings of Brandes. The amount of atrophy was found to be proportional to the degree of fixation secured for the part. Rarefaction and a loss of the finer structural detail, furthermore, were observed at a very early date. Brandes reports changes at the end of eight days in cases in which the Achillis tendon had been cut. In the experiments cited here the earliest changes were noted on the fourth day after immobilization.

The combination of fixation and slight local anæmia, as planned in Experiment XIII, seemed to exert no accelerating influence on the process of bone absorption. Nor was any increase in the rate of the changes found, when to the immobilization in plaster was added a transection of the nerve supplying the foreleg—Experiment XIV. The fixation secured by the cast probably exceeded that which resulted from the nerve division; the hip muscles certainly were more active in the latter. When clinical cases exhibiting atrophy of a non-infectious type are analyzed and the confusing conception of trophic influences dispelled, the inactivity element is found to play a very prominent part. Atrophies of this type are frequently overlooked, as Sudeck, Brandes and others have pointed out.

The fact that fixation leads to atrophic changes in the immobilized limb indicates the importance of functional activity in the normal nutrition of bone. While numerous writers

explain this atrophy by the fact that organs in general receive less blood supply when they are kept at rest, it was pointed out in an earlier paragraph that there is much evidence against such a view. Certain experiences in bone transplantation, furthermore, suggest that the blood supply is only one of the factors responsible for the survival of the graft. Murphy,[16] Phemister,[19] Davis and Hunnicutt [5] and others have shown that when bone is transplanted into soft parts—muscle, fat, etc.—little or no proliferation occurs and the graft is gradually absorbed. The opportunities for establishing a new blood supply in muscle, of course, are excellent. It seems improbable that such a transplant ultimately perishes through want of the proper nourishment. What does appear likely is that bone transplanted into such an environment atrophies and disappears, because it has ceased to receive the functional stimuli normal to osseous tissue in general.

A somewhat similar factor appears to be necessary for the activity and growth of certain more highly specialized tissues. In transplanting pieces of thyroid Halsted [9] has pointed out that the grafts will take only when there is a deficit of thyroid tissue in the body. This may be interpreted to mean that the transplants require a functional stimulus to survive.

IMMOBILIZATION AND BONE REPAIR.

EXP. XV.—*Dog No.* 7.—A hole from 4 to 5 mm. in diameter was drilled through each radius in an antero-posterior direction. Care was taken not to injure any nerves or vessels and to make the steps of the operation similar on the two sides. The right foreleg was then immobilized in plaster to prevent the dog from using it in standing, walking, etc. The opposite limb was left unbandaged. Healing *per primam*.

A Roentgen-ray examination on the following day showed a clear cut, circular defect in each radius. It was likewise noted that the cortex and medulla of each bone in the foreleg on either side cast corresponding shadows. Two weeks later the dark spot made by the defect in the right tibia showed no appreciable change; that in the left leg, however, was slightly cloudy indicating a more active process of repair on this side. Subsequent examinations showed a considerably slower progress in healing on the immobilized side. Slight structural changes in the tibia and fibula pointing to an inactivity atrophy were noted about the fourth week. This process advanced slowly throughout the experiment.

Discussion.—Since immobilization plays an important rôle in the development of atrophy, it is fair to suppose that it likewise influences the rate of repair in fractures and other bone injuries—presumably by delaying the formation of callus. Some have assumed that absolute rest is essential to the repair of bone, just as it is favorable to the healing of wounds elsewhere in the body. Others, however, while recognizing the necessity for the maintenance of a proper alignment of the fragments, have held that perfect fixation in itself is unfavorable to the most rapid healing.

In order to obtain more light on this problem Experiment XV was carried out. Since actual fracture of the tibiæ would have entailed the use of splints on either foot it was found advisable to make use of the expedient described above whereby exactly similar amounts of repair were called for in the two limbs.

The delayed healing on the immobilized side suggests that the factors which are directly responsible for the changes characteristic of simple disuse atrophy are also active when a part is fixed in splints or plaster in treatment for fractures. This may explain in a measure the sluggishness of healing noted in certain cases of fracture, for it is well known that the degree of inactivity atrophy may be greater in one subject than in another, subsequently to the same period of immobilization.

CONCLUSIONS.

I. A destruction of the sensory nerves to a part occasions no direct local atrophy of bone. A destruction of the motor nerves, on the other hand, leads to a certain amount of atrophy. This, however, is indirectly the result of inactivity or disuse and is directly proportional in extent to the degree of paralysis present in the part.

II. Local venous congestion leads directly to no recognizable changes in the structure of bone. Local anæmia due to injury to the arterial supply, except in an extreme degree, likewise occasions no bone atrophy so long as the part remains functionally active.

III. Inactivity atrophy may appear very soon after immobilization of a limb—as early as the fourth or fifth day in rabbits. It is probably due to a decrease or to an absence of the functional stimuli necessary to the normal nutrition of bone.

IV. Immobilization retards the process of repair in bone injuries.

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NOTE ON THE ORIGIN OF THE LACTIC ACID BACTERIA IN MILK

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It has recently been shown by Shippen[1] that the principal organism concerned in the normal souring of milk in Baltimore is the species known usually as *Streptococcus lacticus*, for which, however, the term *Bacterium güntherii*, Lehmann and Neumann, he regards as the correct designation. This species occurred in nearly all the samples of milk examined by Shippen, and in the majority of instances was the predominant one.

In view of Shippen's findings it becomes a matter of interest to determine the ultimate source of this species in nature. Three different possible places have been suggested from which the organism could find a ready entrance into milk. It has been suggested: (1) that the species is a normal inhabitant of the cow's udder, in which event it would, in all probability, always be present in milk; (2) that the species is a regular constituent of the cow's saliva, in which event it would find its way into milk from the cow's udder whenever the animal was not prevented from licking the udder with her tongue; finally (3) that the organism is a constituent of the dung, and consequently would always appear in the milk when proper precautions were not carried out to prevent the contamination of the milk by fæcal material. The present inquiry relates only to the third of these hypotheses, namely, the question of the presence of *Streptococcus lacticus* in cow dung and its relative frequency there.

Two different methods were employed for the isolation of this organism. In the first method plates of litmus-dextrose-agar were poured directly from the dejecta, incubated 24-48 hours, and the small, fine colonies thought to be *Streptococcus lacticus* picked up, transferred to agar, subcultured and identified. The essential points necessary for the identification of this species, as indicated by Shippen, were kept clearly in mind and only those organisms exhibiting these cardinal features were regarded as *Bact. güntherii*. In the second method, a series of litmus-milk tubes was inoculated with small particles from the dejecta with the expectation that this species would show an especial predilection for milk, developing there to the exclusion of other organisms. From these milk tubes showing the characteristic acidification and coagulation, plates were now poured on litmus-dextrose-agar and the typical colonies fished. By the use of both methods it was shown that the lactic acid organisms are constantly present in cow-dung. In 7 consecutive samples they were isolated in each case and by both methods. They were, however, by no means abundant and did not constitute the main predominating species.

The attempt was now made to gain some approximate idea as to the numerical ratio that these organisms bear to the other bacteria in the bovine dejecta. To determine this point 1 cc. of the dejecta was suspended in 100 cc. of sterile water from which dilutions were made and quantities of the emulsion varying from 0.1 to 0.0001 cc. plated in litmus-dextrose-agar. It was found that the plates poured from the 0.01 cc. dilution were fairly thickly seeded and yet contained many isolated colonies. One hundred colonies from the 0.01 cc. plate were now fished, transferred to agar, subcultured and identified. The percentage of the various organisms in each sample was thus roughly obtained. The relative numbers of *Streptococcus lacticus* varied from 4 to 12 per cent, as can be seen in the following table. In but one instance (sample 6) was the organism lacking from the plates.

Samples.	Organisms.	Percentage of Occurrence.
1.	Coli-aerogenes group	96
	Streptococcus lacticus	4
2.	Coli-aerogenes group	85
	Yellow staphylococcus	4
	Streptococcus lacticus	12
3.	Coli-aerogenes group	88
	Bacillus subtilis	4
	Bacillus megatherium	4
	Streptococcus lacticus	4
4.	Coli-aerogenes group	72
	White staphylococcus	8
	Bacillus megatherium	4
	Bacillus petasites	4
	Bacillus mesentericus fuscus	4
	Streptococcus lacticus	8
5.	Coli-aerogenes group	80
	Unidentified bacilli	12
	Streptococcus lacticus	8
6.	Coli-aerogenes group	12
	Unidentified bacilli	84
	Bacillus megatherium	4
7.	Coli-aerogenes group	72
	Bacillus subtilis	8
	Yellow staphylococcus	4
	Unidentified bacilli	8
	Streptococcus lacticus	8

CONCLUSION.

As previously shown by Esten,[2] the lactic acid organism known usually as *Streptococcus lacticus* is a normal constituent of cow dung. While its presence in other regions in the animal has been indicatel by others, in view of these findings the possibility must be borne in mind that the lactic acid organisms in milk have one constant source of origin in the dejecta of the animal.

[1] Shippen: Principal Types of Organisms in Baltimore Milk. The Johns Hosp. Bull., April, 1914, XXV, No. 278.

[2] Esten: Bacterium lactis acidi and its sources. Bulletin No. 59, Starr's Agricultural Experiment Station, August, 1909.

NOTES ON NEW BOOKS.

Obstetrical Nursing. By CHARLES SUMNER BACON, Ph. D., M. D. Cloth, $2.00. *(Philadelphia: Lea & Febiger, 1915.)*

This is an exceedingly helpful reference book on obstetrics—far above the average in regard to practical advice, and with some very sensible ethical notes.

The care of the patient during pregnancy and the puerperium is fully and clearly considered, as well as the complications that might arise and the treatment expected of the nurse in each instance.

While the author realizes, as he remarks in the preface, that the nurse should have a comprehensive knowledge of the scientific side, he does not take up the pelvic anatomy, ovum, or mechanism of labor, clearly or fully enough to make the book of value as a text-book. He also devotes very little time to the disturbances of metabolism as compared with his consideration of the other derangements and abnormalities of pregnancy.

The book would be a helpful addition to a nurse's library.

E. A. T.

Students' Manual of Gynecology. By JOHN OSBORN POLAK, M. S. C., M. D., F. A. C. S. *(Philadelphia and New York: Lea & Febiger, 1915.)*

An attempt to reduce any subject to manual form is always a difficult task and usually results in an incomplete volume. Dr. Polak's work is no exception. The subject-matter is well arranged, but the descriptions are very brief and not infrequently important conditions are dismissed with a single statement. The illustrations are numerous but very diagrammatic. J. C. N.

The Tenth and Eleventh Reports of the Henry Phipps Institute, of Philadelphia, 1915. Published by the Henry Phipps Institute, Philadelphia.

These reports are of great interest. The Tenth contains an article on Pulmonary Acoustic Phenomena by C. M. Montgomery, M. D., of the Henry Phipps Institute, and E. A. Eckhardt, Ph. D., of the Department of Physics, University of Pennsylvania. The study has been dealt with under two main headings, namely, "The Voice Sounds, Spoken and Whispered," and "The Respiratory or Breath Sounds," and a summary completes this excellent article. Seldom has this subject been treated more fully or carefully, and it should be of the greatest value and help not only to the student and general practitioner, but also to the physician who is specializing in diseases of the lungs, especially if he is teaching students.

The Eleventh Report deals with the "Study of the Housing and Social Conditions in Selected Districts of Philadelphia," by Frank A Craig, M. D., Instructor in Medicine. Two questions are considered, namely, "Housing" and "Living Conditions." Under the head of "Housing" are included "Grading of Houses According to the Special Classification," "Housing in Detail," "Summary of Housing" and "Importance of Good Housing and Its Relation to the Health of the Public."

"Living Conditions" are considered from the standpoint of "Social Status of Families Studied," "Crowding," "Rent," and "Nationality." The author has been impressed by the inadequate measures adopted to protect the public against disease. He feels that the analogy between crime and disease is a very close one, and that education of the public is essential, there being one large portion of the population for whom education alone is sufficient to prevent them from performing acts prejudicial to the public welfare, but that the remainder are prevented from such acts only by police supervision. Hence he holds that the problem of the health of the public will never be solved until a vigorous, widespread campaign of education has reached the first, and sanitary police, or inspectors with police powers, are provided for the second group. The article contains numerous valuable charts and an instructive map of the part of the city studied. The report is well presented and should prove very valuable.

K. H. V.

Therapeutics of the Circulation. By SIR LAUDER BRUNTON, M. D., F. R. S., F. R. C. P. Second edition, $2.50 net. *(New York: Paul B. Hoeber, 1914.)*

In 1908 Sir Lauder Brunton published a series of eight lectures that he had delivered three years before in the Physiological Laboratory of the University of London. They were presented in accordance with the general purpose of the University to have recent investigators describe their own researches. These particular lectures were very generally devoted to physiology and pharmacology, and were abundantly illustrated from the author's rich experience in experimental investigation. No effort was made to discuss problems other than those which had occupied the especial attention of Sir Lauder. The results, therefore, did not develop a text-book, but constituted individual chapters in the domain of experimental physiology, with interesting remarks on practical therapeutics that followed therefrom.

In 1914 a completely revised edition was published which, however, is based on the preceding volume. There is still an immense amount of interesting physiological facts concerning the organs of circulation, with an absence of any system in the developing of such studies. Therapeutics becomes a very prominent feature, but is distinctly subordinate, as it should be, to physiology, which supplies the reasons for many therapeutic procedures. The drugs discussed belong rather to the past generation in the large number and complex combinations employed; but, withal, they are distinctly regarded as adjuvants to the fundamental methods of treatment—rest, nutrition, and elimination.

The physiology and pharmacology contained in the book makes it instructive and valuable—a storehouse of concise reasoning and adequate explanation in the science of the physiology of the vascular system. The book, while not so systematic and while partially devoted to therapeusis, is comparable to Krehl's Pathological Physiology in its effort to develop a fundamental understanding of cardiac knowledge and investigation.

Therapeutics of the Circulation is published in a small pocket-sized volume of five hundred pages, with fair type, an abundant index, and an excellent bibliography. While not a text-book nor a satisfactory reference volume, it is an example of "summer reading" that could be perused equally advantageously by the second-year student or the active practitioner, who would gain an understanding of many physiological discussions, and especially a comprehension of a rational therapeutics in so far as therapeutics has a physiological basis. E. W. B.

Osler's Modern Medicine. Vol. V. Diseases of the Nervous System; Diseases of the Locomotor System. $5.00 net. *(Philadelphia: Lea & Febiger, 1915.)*

This volume comprises practically the same subjects as Vol. VII in the first edition, and shows with the preceding volumes of the second edition the improvements in format, letter press and illustrations. The articles are by men whose names are familiar to the English speaking world, and reach a very high average of excellence. Especially noteworthy are Barker's introduction, Cushing on tumors of the brain and meninges, Thomas on diseases of the cerebral blood-vessels, and Spiller on the motor tract.

The second division includes myositis and Thomsen's disease

by Steiner, arthritis deformans by McCrae, which is transposed from the motor and trophic group of the first edition, osteomalacia by Dock, and the rarer dystrophies and plastic disturbances of the bones by Emerson.

The general index covers 63 pages and is very well arranged. The second edition, as a whole, is much more attractive than the first, and while it lacks some of the references and historical material of the original issue, it will prove the most generally acceptable system in English. T. R. B.

International Clinics. Vol. III. Twenty-fourth Series. Edited by HENRY W. CATTELL, M. D., and associates. Cloth, $2.00. *(Philadelphia and London: J. B. Lippincott Company, 1914.)*

This volume contains 26 papers on a variety of medical and surgical subjects. Worthy of mention are the articles by Dederick on malaria carriers; by Pemberton, on the treatment of rheumatic arthritis; and by Hess, on the use of vaccines in pertussis. The leading article is devoted to the surgical practice of John B. Deaver, of Philadelphia, covering briefly the operative treatment of about 120 selected cases from his clinic.

With the exception of these articles there is little of interest in the volume. The papers on the treatment of pulmonary tuberculosis and of diabetes mellitus are particularly poor and are commendable only because of their brevity. P. W. C.

Balneo-Gymnastic Treatment of Chronic Diseases of the Heart. By PROF. THEODOR SCHOTT, Bad Nauheim. Pages 191; 87 illustrations and charts. Cloth, $2.50. *(Philadelphia: P. Blakiston's Son & Co., 1914.)*

This book gives a description of the methods of treatment in use at Bad Nauheim.

The chapters on the general treatment of cardiac disorders contain but little unknown to the average practitioner; while those devoted to balneo-therapy give one the impression that the results quoted are obtained as much from the general routine of a carefully-regulated mode of life with suitable dietary and a complete change of surroundings as from any special virtue in the bath. Artificial imitation of the waters is discouraged and the directions for the preparation of effervescing baths in the home are of the most general character.

The chapters on gymnastic treatment, however, are excellent, the resistance exercises being well described and illustrated by numerous photographs with descriptive letter-press. For these we owe Prof. Schott a considerable debt of gratitude. D. S. L.

Food Products. By HENRY C. SHERMAN, Ph. D., Professor of Food Chemistry, Columbia University, New York. *(The Macmillan Company, 1914.)*

Those who wish to be oriented on food legislation, its preparation, composition and nutritive value, cannot do better than to supplement their studies with this book. It summarizes in a very lucid manner much of the far-scattered effort of the lawmakers and scientists. Especial attention has been paid to the very valuable researches and data gathered by the various state agricultural experiment stations and the United States Department of Agriculture. Most of these publications are far too little known and have not had the prominence and general use they deserve. In this book many of them are referred to, and thus a large field of reference is opened to the reader. Some of the food tables given do not differ from those printed hundreds of times before; those, however, dealing with the excess of acid and base-forming elements, with the ash constituents and with the weight of food in 100 caloric portions, form welcome additions to the dietary tables now available. From a medical point of view, practical tables have yet to be compiled. The present book is a distinct aid in this direction even if it does not solve the problem completely. H. O. M.

Diabetes Mellitus. Designed for the Use of Practitioners of Medicine. By NELLIS B. FOSTER, M. D. *(Philadelphia and London: J. B. Lippincott Company, 1915.)*

The long-continued interest of the author in diabetes and his personal contributions to our knowledge of the disease well qualify him for presenting this little volume for the use of practitioners of medicine.

Few of the commoner diseases met with are more wretchedly handled by the general practitioner than is diabetes, owing to the fact that he fails to grasp the basic metabolic disturbances which lie at the foundation of the disease. He usually feels that his duty to his patient has been discharged when he has prescribed a diet in which the carbohydrates are restricted or cut off and has then ordered a certain amount of gluten bread, made from one of the numerous gluten flours on the market, all of which are notoriously unreliable and practically all of which are rich in starch. Rarely does he think of watching for evidences of diabetic acidosis, which constitutes the most serious complication of the disease.

The author endeavors to give an unbiased critical judgment of the various theories that have been advanced from time to time to explain the cause of diabetes. It is of interest to note that he is strongly opposed to the theory of von Noorden and his school, that most, if not all, cases are dependent upon some disturbance in the co-relationship of the action of the hormones of the various ductless glands.

Chapters are presented on normal metabolism, sources of glucose in the animal body, experimental glycosuria, acidosis, pathogenesis, history, etiology, pathology, symptomatology, renal diabetes, diagnosis and course of the disease, total metabolism in diabetes, treatment, and identification of sugars in the urine.

The subject matter is concisely and clearly treated in 243 pages, and although the present work adds one more to the long list of books on this subject, its excellence justifies its appearance and it ought to serve a useful purpose in helping the practitioner to handle the much-abused sufferers from this disease. T. B. F.

BOOKS RECEIVED.

Association of American Physicians. Transactions of the Association of American Physicians. Volume XXIX. 1914. 8°. 679 pages. Printed for the Association. Philadelphia.

Tics and Their Treatment. By Henry Meige and E. Feindel. With a Preface by Professor Brissaud. Translated and edited, with a critical appendix, by S. A. K. Wilson, M. A., M. B., B. Sc. 1907. 80°. 386 pages. William Wood & Co., New York.

Alveolodental Pyorrhea. By Charles C. Bass, M. D., and Foster M. Johns, M. D. Illustrated. 1915. 8°. 167 pages. W. B. Saunders Company, Philadelphia and London.

Studies from the Rockefeller Institute for Medical Research. Reprints, volume XXI. 1915. 8°. 637 pages. The Rockefeller Institute for Medical Research, New York.

Diarrheal, Inflammatory, Obstructive, and Parasitic Diseases of the Gastro-Intestinal Tract. By Samuel Goodwin Gant, M. D., LL. D. Illustrated. 1915. 8°. 604 pages. W. B. Saunders Company, Philadelphia and London.

Collected Papers of the Mayo Clinic, Rochester, Minnesota. Edited by Mrs. M. H. Mellish. Volume VI, 1914. 1915. 8°. 814 pages. W. B. Saunders Company, Philadelphia and London.

The Treatment of Fractures. With Notes Upon a Few Common Dislocations. By Charles Locke Scudder, M. D. Eighth edition, revised, with 1057 illustrations. 1915. 8°. 734 pages. W. B. Saunders Company, Philadelphia and London.

X-Rays. How to Produce and Interpret Them. By Harold Mowat, M. D. Edinburgh. 1915. 8°. 204 pages. Henry Frowde and Hodder & Stoughton, London.

American Pediatric Society. Transactions of the American Pediatric Society. Edited by Linnaeus Edford La Fétra, M. D. Volume XXVI. 1914. 8°. 362 pages. [American Medical Association Press, Chicago.]

Modern Aspects of the Circulation in Health and Disease. By Carl J. Wiggers, M. D. Illustrated with 104 engravings. 1915. 8°. 376 pages. Lea & Febiger, Philadelphia and New York.

Applied Immunology. The Practical Application of Sera and Bacterins Prophylactically, Diagnostically and Therapeutically, with an appendix on Serum Treatment of Hemorrhage, Organotherapy and Chemotherapy. By B. A. Thomas, A. M., M. D., and R. H. Ivy, M. D., D. D. S. Five colored inserts and 68 illustrations in text. 1915. 8°. 359 pages. J. B. Lippincott Company, Philadelphia and London.

Simplified Infant Feeding. With 75 Illustrative Cases. By Roger H. Dennett, B. S., M. D. With four illustrations. 1915. 8°. 355 pages. J. B. Lippincott Company, Philadelphia and London.

The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago. Volume IV, No. 3. June, 1915. 8°. W. B. Saunders Company, Philadelphia and London.

The Medical Clinics of Chicago. Vol. I, No. 1. July, 1915. 8°. W. B. Saunders Company, Philadelphia and London.

The Ductless Glandular Diseases. By Wilhelm Falta. Translated and edited by Milton K. Myers, M. D. With a foreword by Archibald E. Garrod, M. D. (Oxon.) F. R. C. P. (Lond.) F. R. S. With 101 illustrations in the text. [1915.] 8°. 673 pages. P. Blakiston's Son & Co., Philadelphia.

The Development of the Human Body. A Manual of Embryology. By J. Playfair McMurrich, A. M., Ph. D., LL. D. Fifth edition, revised and enlarged, with 287 illustrations, several of which are printed in colors. [1915.] 12°. 493 pages. P. Blakiston's Son & Co., Philadelphia.

Senescence and Rejuvenescence. By Charles Manning Child. [1915.] 8°. 481 pages. The University of Chicago Press, Chicago, Ill.

Collected Papers from the Research Laboratory Parke, Davis & Co. Detroit, Mich. Dr. E. M. Houghton, Director. Reprints. Vol. III. 1915. 8°. 341 pages.

A Text-Book of Surgery. By George Emerson Brewer, A. M., M. D. Assisted by Adrian V. S. Lambert, M. D., and by members of the Surgical Teaching Staff of Columbia University. Third and enlarged edition, thoroughly revised and rewritten. Illustrated with 500 engravings in the text and 23 plates in colors and monochrome. 1915. 8°. 1027 pages. Lea & Febiger, Philadelphia and New York.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W Cattell, A. M., M. D. Volume III. Twenty-fifth series. 1915. 8°. 303 pages. J B. Lippincott Company, Philadelphia and London.

Diseases of the Arteries, Including Angina Pectoris. By Sir Clifford Allbutt, K. C. B., M. A., M. D., F. R. C. P., F. R. S., Hon. M. D., LL. D., D. Sc. In two volumes. 1915. 8°. 534; 559 pages. Macmillan & Co., Limited, London.

Amnesia and Analgesia in Parturition (Twilight Sleep). By Alfred M. Hellman, B. A., M. D., F. A. C. S. 1915. 12°. 197 pages. Paul B. Hoeber, New York.

Twelve Lectures on the Modern Treatment of Gonorrhea in the Male. By Dr. P. Asch. Translated and annotated by Faxton E. Gardner, M. D. Illustrated. 1915. 8°. 104 pages. Rebman Company [New York].

The Book of the Fly. A Nature Study of the House-Fly and Its Kin, the Fly Plague and a Cure. By G. Huristone Hardy. With an introduction by Halford Ross. [1915.] 12°. 124 pages. Rebman Company, New York.

A Text-Book of Histology. By Rudolph Krause. Translated from an original manuscript and printed only in the English language. With 36 illustrations in the text, three of which are colored. The references to illustrations given in the text relate to the colored illustrations contained and published in Dr. Rudolf Krause's "A Course in Normal Histology." [1915.] 8°. 274 pages. Rebman Company, New York.

Praktikum der Chirurgie. Ein Leitfaden für Aerzte, chirurgische Assistenten und Medizinalpraktikanten. By Dr O. Nordmann. II Teil. Spezielle Chirurgie. Mit 161 teils farbigen Abbildungen. 1915. 8°. 632 pages. Urban & Schwarzenberg, Berlin and Wien.

Die Therapie der Haut—und venerischen Krankheiten mit besonderer Berücksichtigung der Behandlungstechnik. Von Prof. Dr. J. Schäffer. Mit 87 Abbildungen im Text. 1915. 8°. 450 pages. Urban & Schwarzenberg, Berlin and Wien.

Student's Text-Book of Hygiene. By W. James Wilson, M. D., D. Sc., D. P. H. [1915.] 8°. 270 pages. Rebman Company, New York.

A Manual of the Practice of Medicine. Prepared especially for Students. By A. A. Stevens, A. M., M. D. Tenth edition, illustrated. 1915. 8°. 629 pages. W. B. Saunders Company, Philadelphia and London.

Exercise in Education and Medicine. By Tait McKenzie, B. A., M. D. Second edition, thoroughly revised, with 478 illustrations. 1915. 8°. 585 pages. W. B. Saunders Company, Philadelphia and London.

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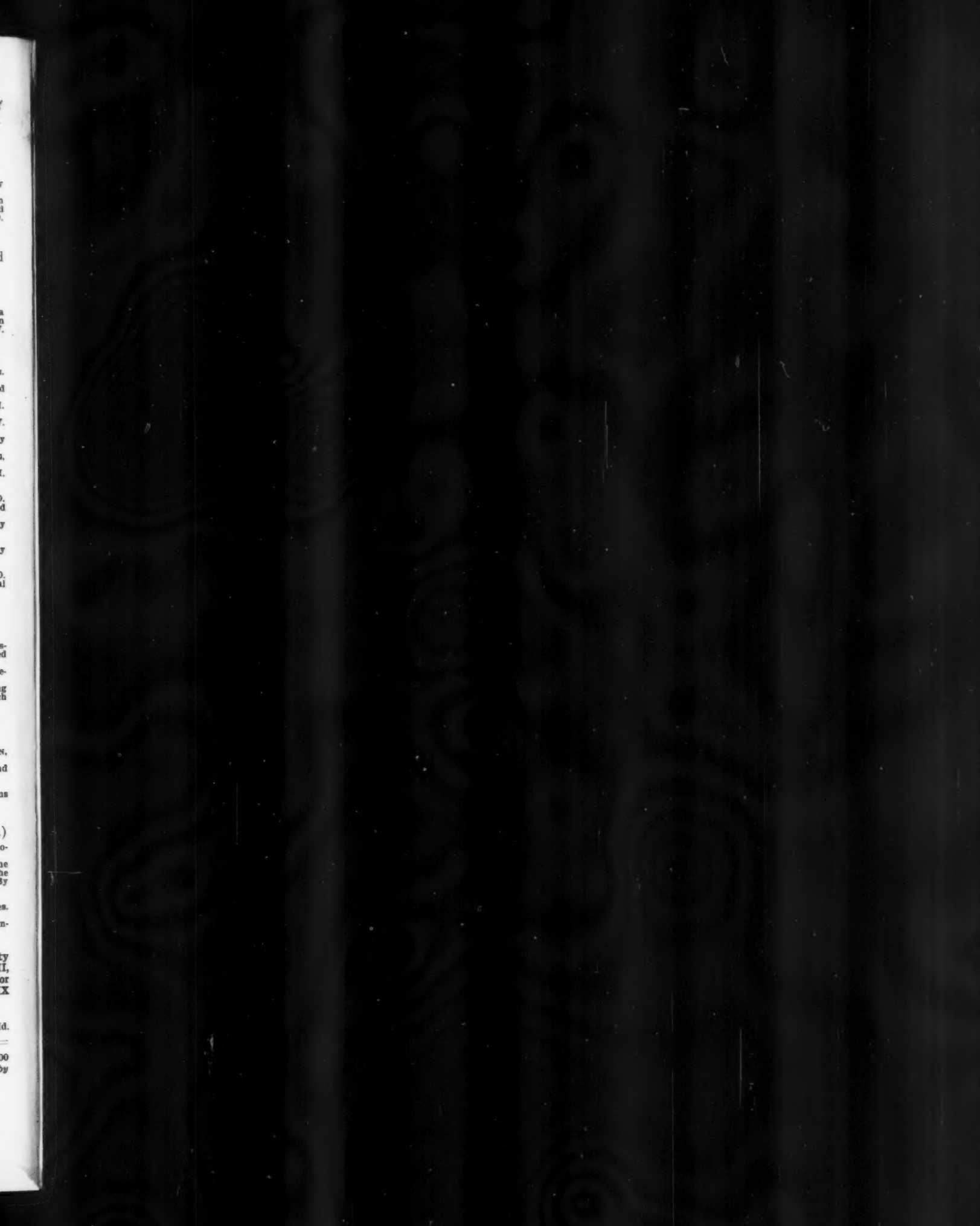
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